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Original Article

Randomized controlled study of pain education in patients receiving radiotherapy for painful bone metastases

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ABSTRACT

Background: Although short-course radiotherapy is an effective treatment for patients with painful bone metastases, pain is not always sufficiently controlled. We therefore investigated the additional effect of a nurse-led pain education program on pain control and quality of life (QoL).

Patients and methods: In this multicenter study, patients with solid tumor bone metastases and a worst pain intensity of ≥5 on a 0–10 numeric rating scale (NRS) were randomized between care as usual (control-group) and care as usual plus the Pain Education Program (PEP-group). PEP consisted of a structured interview and personalized education with follow-up phone calls. Patients completed the Brief Pain Inventory, EORTC QLQ-C15-PAL and BM22 at week 0, 1, 4, 8 and 12. The primary outcome was pain control, defined as the number of patients whose worst pain intensity was <5 on a 0–10 NRS after 12 weeks. Secondary outcomes were time to reach control of pain (NRS < 5), mean worst pain and average pain, and QoL at weeks 1, 4, 8 and 12.

Results: Of 308 included patients, 182 (92 PEP-group) completed 12 weeks follow-up. At 12 weeks, more patients in the PEP-group (71%) compared to the control-group (52%) reported pain control (P =.008). In the PEP-group, pain control was reached earlier than in the control-group (median 29 days versus 56 days; P =.003). Mean worst and average pain decreased in both groups but decreased more in the PEP-group. QoL did not differ between the groups.

Conclusion: The addition of PEP to care as usual for patients treated with radiotherapy for painful bone metastases resulted in less pain and faster pain control.

Most patients with advanced cancer suffer from pain [1], often due to bone metastases (31%–42%) [2]. A single fraction of 8 Gray (Gy) radiotherapy is the standard therapy for most patients with uncomplicated painful bone metastases, with a response rate of 61%-71% within four weeks [3–5]. However, about one-third of patients still experience pain after radiotherapy and need additional pain management. Retreatment is possible, but the response rates (maximum 50%) are lower [6]. This poses a significant problem as uncontrolled pain is associated with lower quality of life (QoL) [7–9].

Inadequate pain management in these patients may be due to profession-related and patient-related barriers. The most important profession-related barriers are inadequate assessment and insufficient knowledge of pain management. Important patient-related barriers include poor knowledge and misconceptions about pain medication and its side-effects, non-adherence to prescribed treatments, and insufficient communication with healthcare practioners [10–11]. Moreover, common misbeliefs, such as fear of addiction to opioids, influence how patients communicate their pain and affect their compliance with pain medication [12].

Patient education regarding pain management is one way to overcome these patient-related barriers [11,13–14]. Several studies have suggested that patient education may improve knowledge, adherence and self-efficacy, resulting in less pain, less interference with daily life, and better QoL. As a result, various pain education

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programs have been developed, with a wide variation in type, content, and duration [11,13,14]. However, it remains unclear which components of these programs contribute to better pain control [11,13–15].

In the Netherlands, a nurse-led pain education program has been tailored to the needs of individual patients. Known as the Pain Education Program (PEP) [16], it enhances patients' knowledge regarding pain and pain treatment. It instructs patients on how to register their pain intensity and encourages help-seeking behavior. A previous randomized controlled trial (RCT) showed that PEP is feasible and effective in patients with chronic cancer pain. After participation in PEP, patients in the intervention group had increased pain knowledge, and those in a subgroup not receiving district nursing services reported decreased pain intensity [16]. In another RCT using the PEP, lower pain intensity in the intervention group was reported after four weeks, but no differences were found after eight weeks. The researchers concluded that follow-up reinforcement by telephone should be implemented to ensure a long-term effect of PEP [17]. PEP might also be effective in patients with painful bone metastases when integrated into standard care during palliative radiotherapy treatment. According to Dutch guidelines, a pain intensity of $\geq$5 on a 0–10 numeric rating scale (NRS; 0 = no pain, 10 = worst pain imaginable) should prompt medical intervention [18].

In a sample of patients with painful bone metastases after treatment with a single fraction or short-course radiotherapy, we conducted a RCT to determine the effect of a nurse-led PEP – with follow-up reinforcement by telephone – on pain control and QoL.

Patients and methods

Patients and study design

In this RCT, patients were included from five Radiotherapy departments at hospitals and medical centers in the Netherlands. Patients were randomized 1:1 to two groups: care as usual (control-group) or care as usual plus PEP and follow-up sessions by telephone (PEP-group). The study was centrally approved by the ethics committee of the University Medical Center Groningen and registered at ClinicalTrials.gov (NCT01358539).

Eligible patients were 18 years or older, had uncomplicated painful bone metastases of a solid tumor, had experienced a self-reported worst pain intensity of $\geq$5 on a 0–10 NRS before single fraction or short-course radiotherapy (1–5 fractions, at the discretion of the treating radiation oncologist), had a life expectancy of $\geq$3 months with a WHO performance status 0–3, and were able to complete questionnaires and follow instructions.

Patients in the control-group received the following information: the standard information provided by their radiation oncologist on treatment goals, the expected effectiveness of the radiotherapy, the possible side effects and their treatment. These patients also received information leaflets addressing radiotherapy, cancer pain (Dutch Cancer Society), and facts and misconceptions regarding opioid use [19]. Additionally, the radiation oncologist contacted the patient (mostly by telephone) 3 to 4 weeks after treatment to evaluate the effect of the radiotherapy.

Besides the above information, patients in the PEP-group participated in one face-to-face education session before starting radiotherapy and four follow-up sessions with a research nurse by telephone after 1, 4, 8 and 12 weeks. At the start of this study, all participating centers pointed out dedicated research nurses trained to conduct the PEP. An adapted version of the PEP [16] was used for the face-to-face session. It consisted of a structured interview, personalized education regarding pharmacological and non-pharmacological pain treatment, erroneous beliefs, self-management, and instructions on using a pain diary (Table 1). During the face-to-face and follow-up sessions, patients were encouraged to contact the medical practitioner who had prescribed their pain medication (general practitioner or oncologist) in case of uncontrolled pain or other questions regarding pain and side effects of analgesics.

The face-to-face educational session lasted 45 to 60 minutes, and relatives were also invited to attend. The follow-up sessions lasted 5 to 15 minutes.

Procedures

Patients were informed about the study by mail before their appointment with the radiation oncologist. During the first visit, they were invited to participate in the study. After providing writ-

Table 1
Main themes in the Pain Education program (PEP).

First consultation	The following themes are discussed: - Information and instruction about pain and pain management: • Definition of pain; • Causes of pain; • Pharmacological pain treatment: name, doses, schedule, mechanism, purpose, procedure, and duration of analgesics and co-analgesics; • Purpose, procedure and duration of invasive pain techniques; • Experienced side-effects related to pain management (e.g. sedation, constipation, nausea and vomiting); • Interference of pain aspects with sleep, mobility, activities, appetite, emotions and how to deal with this; • Effect of non-adherence; • Use of non-pharmacological pain management techniques (e.g. cold, heat, massage, relaxation). Patients are asked to give their ideas on the following eight statements to investigate any myths and misconceptions: 1. Cancer pain can be relieved effectively; 2. Pain medication should be given only when pain is severe; 3. Most cancer patients will become addicted to pain medication; 4. It is better to give the lowest amount of pain medication, so that larger doses can be used later if pain increases; 5. It is better to give pain medication around the clock than only when needed; 6. Non-pharmacological interventions can relieve pain; 7. Patients are often overmedicated; 8. Use of pain medication can be changed without consulting a physician. Patients are asked whether they completely agree-completely disagree on a 5 point Likert scale. Improving self-efficacy and help-seeking behavior with regard to pain and pain management: - Patients are invited to start self-record their pain in a pain diary to gain more insight into the course of their pain; - Patients are invited to think about what to do when they experience increased pain; - What actions to undertake if pain is not relieved adequately at home; - Communication with health care providers with regard to pain.
Follow up consultation	During the follow up consultations patients are asked how they cope and if necessary the themes above are repeated.

ten informed consent, stratified randomization per participating center was performed by the Netherlands Comprehensive Cancer Organization (IKNL). The research nurse explained the details of the study procedures to the participating patients. Before the start of radiotherapy, patients completed questionnaires regarding pain and QoL. They also completed these questionnaires at home at week 1, 4, 8 and 12. If patients died during the study period, the questionnaires were completed until death. Patients received the first set of follow-up questionnaires from the research nurse when they were at the radiotherapy department for consultation and were requested to complete these questionnaires seven days after the single or first radiotherapy fraction. The IKNL sent the subsequent questionnaires by mail to the patients' homes. Completed questionnaires were processed by the IKNL, where central data management took place. Reminders were sent once to patients who did not complete their follow-up questionnaires.

The set of questionnaires consisted of the Brief Pain Inventory (BPI), the European Organisation of Research and Treatment of Cancer Quality Of Life Questionnaire Core 15 Palliative Care (EORTC QLQ-C15-PAL) and the corresponding module for patients with bone metastases (EORTC QLQ-BM22). The BPI is a validated questionnaire to assess the location of pain, pain intensity (NRS 0-10 for worst and average pain during the last three days and current pain), used pain medication, and pain relief in the past 24 hours [20]. The EORTC-QLQ-C15-PAL, a short version of the EORTC-QLQ-C30, includes scales and single items on physical and emotional functioning, fatigue, pain, nausea, appetite, dyspnea, constipation, sleeping difficulties, interference with daily activities, and overall QoL [21]. The EORTC-QLQ-BM22 addresses symptoms related to bone metastases and additional QoL dimensions. This 22-item questionnaire comprises four scales: painful sites, pain characteristics, functional interference, and psychosocial aspects [22]. All subscales and single items of the EORTC QLQ-C15-PAL and the EORTC QLQ-BM22 questionnaires were converted to a score from 0-100, with a higher score indicating a higher level of symptoms or functioning.

For each patient, baseline patient and disease characteristics (gender, age, marital status, children at home, level of education, WHO performance status, site of primary tumor, distant metastases other than bone metastases, prior treatment of malignancy, single or multiple fractions radiotherapy given, previous radiotherapy on same bone metastasis and use of pain medication) were collected from their medical records.

Initially, patients were requested to complete the pain and QoL questionnaires weekly. However, after 15 patients were included this turned out to be overly burdensome for the patients. Therefore, the study design was amended (November 24, 2011), with follow-up questionnaires at week 1, 4, 8 and 12. Of the patients who completed the questionnaires weekly, only the questionnaires of week 1, 4, 8 and 12 were analyzed.

Outcomes

The primary outcome was pain control, defined as the number of patients whose worst pain intensity was <5 on a 0–10 NRS after 12 weeks. Secondary outcomes were time to reach control of pain (defined as the first moment of a worst NRS < 5), mean worst and average pain intensity and QoL measures at weeks 1, 4, 8 and 12. The relation between pain intensity, QoL, and predictors of response to PEP was also studied.

Sample size

Sample size calculation was based on data from the Dutch Bone Metastasis Study (DBMS) published in 1999 [4,23]. In that study, 35% of 1157 patients failed to reach a NRS < 5 within 12 weeks after a single fraction or short-course radiotherapy for painful bone metastases. Considering that pain treatment has improved over the last 10 years, we estimated a prevalence of 25% of patients with a mean worst pain intensity $\geq$ 5 during the first 12 weeks after radiotherapy. To detect a reduction to 10%, we calculated that 89 evaluable patients per treatment group were required to reach a power of 80% given a significance level of 5% (1-sided). In the DBMS 25% of the included patients died within 12 weeks. Per treatment group, 139 patients were needed to have data from 89 evaluable patients, assuming 25% drop-out due to death and 25% drop-out due to loss of follow-up.

Statistical analysis

Descriptive statistics were used to describe patient and disease characteristics. The Fisher exact test (1-sided) was used to compare both groups for categorical variables. Time to reach pain control was estimated by the Kaplan Meier method and tested with the log-rank test following the intention-to-treat principle. Analysis of variance (ANOVA) was used to compare group means of the QoL measures at 12 weeks.

We performed logistic regression analysis with the binary variable controlled pain within 12 weeks as a dependent factor and potential predictive factors (age, gender, marital status, level of education, site of the primary tumor, WHO performance status, and use of pain medication (strong opioids or not). Data analyses were done on an intention-to-treat basis using STATA (version 14.2, StataCorp Texas) and SPSS (version 23), using a significance level of 0.05.

Results

In total, 354 patients were included between March 2011 and April 2016: 176 were randomized to the PEP-group and 178 to the control-group. Of the total sample, 46 patients were excluded from the analysis: 38 failed to meet all criteria, mainly because their self-reported worst pain intensity was <5, or the scheduled radiotherapy was canceled or more than 5 fractions were given. Eight patients refused participation immediately after randomization and before completing a questionnaire (Fig. 1). Of the 308 evaluable patients, 92 patients (59%) in the PEP-group and 90 patients (59%) in the control-group completed all 12 weeks of follow-up (Fig. 1). During the follow-up, 60 patients died (26 PEP-group, 34 control-group), and 66 stopped participation (38 PEP-group and 28 in the control-group), mainly due to their worsening condition, which made further participation too burdensome.

Patient and disease characteristics at baseline for the evaluable patients and the patients who completed 12 weeks are presented in Table 2. The mean worst pain intensity was 7.2 (standard deviation (SD) 1.3) in both groups. The mean average pain intensity at baseline was 5.6 (SD 1.1) in the PEP-group and 5.5 (SD 1.6) in the control-group. About half of the patients used strong opioids at baseline (Table 2). Single fraction radiotherapy was given in 66% of the patients in the PEP-group and in 78% of the patients in the control-group. The first or single fraction radiotherapy was started on the same day as randomization or the next day in 66% of the patients and within 1 week in 95% of all patients (range 0–21 days).

Of the patients who completed 12 weeks, more patients in the PEP-group (71%) than in the control-group (52%) reported controlled pain at 12 weeks (P =.008). The median time to reach pain control was 29 days in the PEP-group and 56 days in the control-group (P =.003, Fig. 2). Fig. 3 shows the mean worst pain and mean average pain at all follow-up time points of the intention-to-treat population. Mean worst pain decreased from 7.2 to 3.5 in the

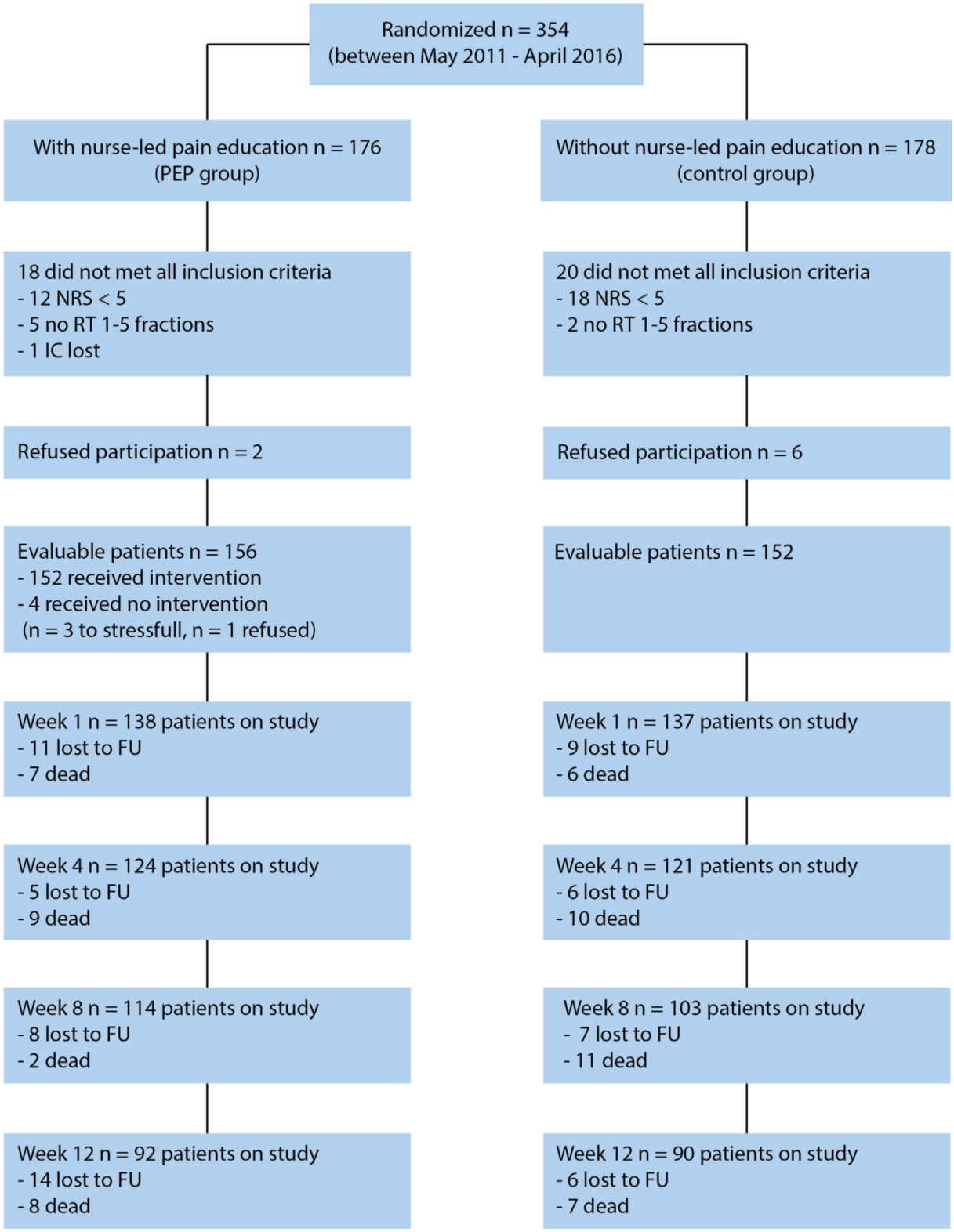

Fig. 1. Flow chart of patients.

PEP-group and from 7.2 to 4.3 in the control-group (P =.0490 between groups at 12 weeks). Mean average pain also decreased in both groups: from 5.6 to 2.8 in the PEP-group and from 5.5 to 3.6 in the control-group (P =.0251 between groups at 12 weeks).

At 12 weeks, there was a clinically significant improvement of functional interference in both groups (EORTC-QLQ-BM22), in the PEP-group from 50.3 to 66.4 and in the control-group from 49.0 to 67.4. There was a slight improvement of psychosocial aspects

Table 2
Patient and disease characteristics at baseline of the randomized patients and the patients who completed follow-up until 12 weeks.

	All analyzed patients		Patients who completed 12 weeks follow-up	
	PEP-group n = 156	Control group n = 152	PEP-group n = 92	Control group n = 90
Gender				
Male (%)	92 (59)	87 (57)	59 (64)	49 (54)
Female (%)	64 (41)	65 (43)	33 (36)	41 (46)
Age (mean ± SD, range)	65.3 ± 10.0, 33–89	65.6 ± 10.2, 37–87	66.0 ± 9.5, 42–87	65.6 ± 10.2, 39–87
Performance status				
WHO 0 (%)	25 (16)	27 (18)	14 (15)	19 (21)
WHO 1 (%)	88 (56)	67 (44)	63 (69)	47 (52)
WHO 2 (%)	36 (23)	46 (30)	12 (13)	20 (22)
WHO 3 (%)	6 (4)	8 (5)	3 (3)	3 (3)
WHO 4 (%)	-	-	-	-
Unknown (%)	1 (1)	4 (3)	-	1 (1)
Marital status				
Single (%)	13 (8)	11 (7)	6 (7)	5 (6)
Married (%)	116 (74)	125 (82)	73 (79)	79 (88)
Living together (unmarried) (%)	7 (5)	4 (3)	2 (2)	1 (1)
Widowed (%)	12 (8)	6 (4)	6 (7)	3 (3)
Other (%)	5 (3)	1 (1)	2 (2)	-
Unknown (%)	3 (2)	5 (3)	3 (3)	2 (2)
Children at home				
No (%)	132 (85)	124 (82)	80 (87)	71 (79)
Yes (%)	24 (15)	26 (17)	12 (13)	19 (21)
Unknown (%)	-	2 (1)	-	-
Level of education				
Lower (%)	44 (28)	53 (35)	23 (25)	29 (32)
Medium (%)	58 (37)	38 (25)	36 (39)	27 (30)
High (%)	46 (30)	53 (35)	29 (32)	31 (34)
Unknown (%)	8 (5)	8 (5)	4 (4)	3 (3)
Primary tumor				
Prostate (%)	57 (37)	37 (24)	41 (45)	24 (27)
Breast (%)	40 (26)	34 (22)	24 (26)	28 (31)
Lung (%)	28 (18)	35 (23)	11 (12)	18 (20)
Colorectal (%)	7 (5)	12 (8)	2 (2)	6 (7)
Kidney (%)	10 (6)	9 (6)	7 (8)	4 (4)
Other (%)	14 (9)	25 (17)	7 (8)	10 (11)
Other metastasis than bone present	71 (46)	97 (64)	33 (36)	54 (60)
Lung (%)	6 (9)	17 (18)	3 (9)	9 (17)
Liver (%)	8 (11)	16 (17)	5 (15)	9 (17)
Lymph nodes (%)	19 (27)	22 (23)	10 (30)	16 (30)
Other (%)	38 (54)	42 (43)	15 (46)	20 (37)
Prior treatment of malignancy				
Surgery (%)	17 (11)	13 (9)	11 (12)	8 (9)
Chemotherapy (%)	15 (10)	16 (11)	6 (7)	10 (11)
Radiotherapy (%)	8 (5)	11 (7)	5 (5)	2 (2)
Hormonal therapy (%)	23 (15)	17 (11)	17 (19)	11 (12)
Combination of therapies (%)	76 (49)	86 (57)	46 (50)	53 (59)
Other (%)	2 (1)	4 (3)	1 (1)	3 (3)
No treatment (%)	13 (8)	5 (3)	5 (5)	3 (3)
Unknown (%)	2 (1)	-	1 (1)	-
Pain score on a 0–10 numeric rating scale (NRS; 0 = no pain, 10 = worst pain imaginable)				
Worst pain (mean ± SD)	7.2 ± 1.3	7.2 ± 1.3	7.1 ± 1.4	7.1 ± 1.4
Average pain (mean ± SD)	5.6 ± 1.8	5.5 ± 1.6	5.5 ± 1.7	5.4 ± 1.6
Radiotherapy treatment				
Single fraction (%)	103 (66)	118 (78)	61 (66)	71 (79)
Multiple fractions (max 5) (%)	53 (34)	34 (22)	31 (34)	19 (21)
Previous radiotherapy on same bone metastasis (%)	25 (16)	25 (16)	16 (17)	14 (16)
Pain medication				
No pain medication (%)	11 (7)	18 (12)	8 (9)	11 (12)
WHO step 1 (no opioids) (%)	48 (31)	40 (26)	36 (39)	35 (39)
WHO step 2 (weak opioids) (%)	17 (11)	15 (10)	10 (11)	11 (12)
WHO step 3 (strong opioids) (%)	80 (51)	79 (52)	38 (41)	33 (37)

(EORTC-QLQ-BM22) and of physical functioning, emotional functioning, and overall QoL (EORTC QLQ-C15-PAL) in both groups (Table 3). There were no statistically significant differences between groups on these aspects at 12 weeks.

Logistic regression analysis showed that age, gender, marital status, level of education, site of the primary tumor, WHO performance status, and use of pain medication did not independently predict which patients benefit from PEP.

Discussion

Palliative cancer care often involves pain control issues. To help address this problem, we performed a randomized clinical trial to determine the effect of a pain education program (PEP) on controlled pain and quality of life in patients with painful bone metastases when added to care as usual for patients treated with a single fraction or short-course radiotherapy. The trial data showed that

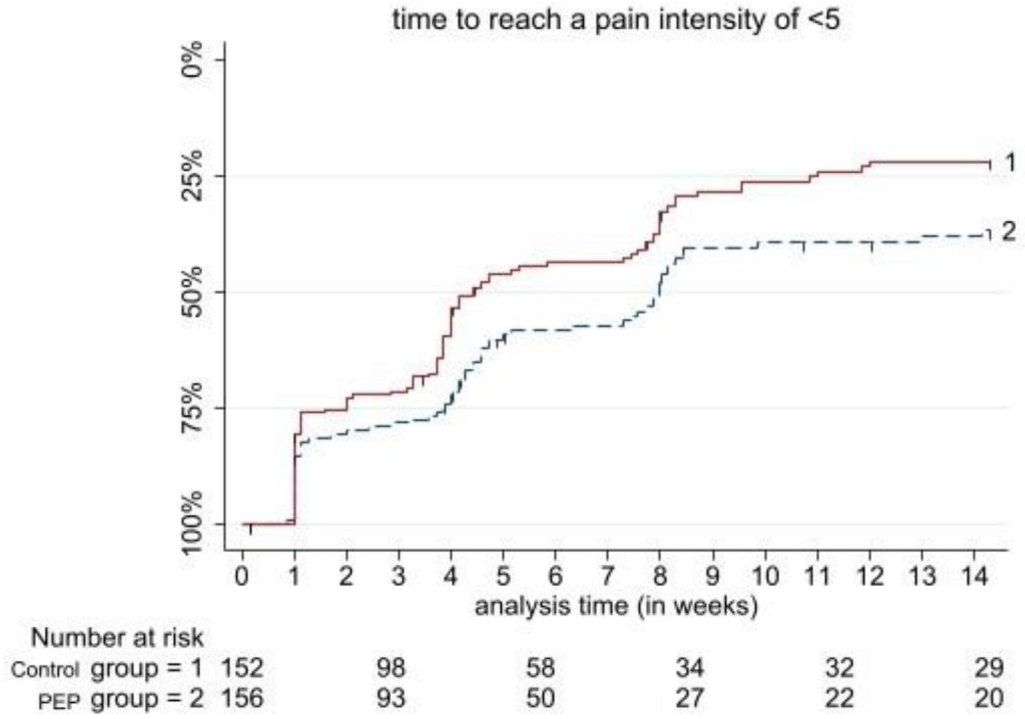

Fig. 2. Kaplan-Meier survival estimates of time to reach a pain intensity < 5. *P* =.003.

the addition of PEP resulted in better pain control 12 weeks after radiotherapy. The percentage of patients with uncontrolled pain was nearly halved in the PEP-group, and pain relief was achieved much faster.

Response to radiotherapy for the treatment of painful bone metastases is defined by the International Bone Metastases Consensus Endpoint Definitions as a decrease in pain intensity by at least two points without analgesic increase, or analgesic reduction of ≥25% with stable or maximally 1 point increase in pain intensity [24]. Consequently, the responses in studies using these endpoints [3–4,6,23–24] differ from our definition of controlled pain. However, the mean worst pain in the control-group at baseline and after 12 weeks of follow-up from our study is comparable to the data from the DBMS [4,23]. Moreover, the study protocol was written in 2010. Since then, a cut-off of ≥4 on the NRS (instead of the ≥5 used in this study) has been implemented in Dutch clinical practice to prompt medical intervention [25].

Our study differed from previous studies using the PEP because we added reinforcement through follow-up sessions by telephone in the intervention during the entire follow-up period and we extended the follow-up to 12 weeks [16,17]. In another RCT using PEP combined with a pain consult, outpatients were phoned every week during 8 weeks of follow-up. This study reported decreased pain intensity for average pain and current pain, but not for worst pain [26]. Together with the findings of our study, this suggests that reinforcement by follow-up sessions is an essential part of pain education programs. However, three other RCTs investigated the effect of educational interventions other than PEP on pain intensity in patients diagnosed with cancer with a follow-up of at least 8 weeks by telephone alone or alternated with face-to-face contact as part of the intervention. No effect of the intervention on pain control was found [27–29]. A possible explanation of the strong effect on pain control in our RCT compared to previous studies could be that education about misconceptions of opioid use in combination with self-reported symptoms and discussing satisfaction during the phone calls has empowered patients in the PEP-group to seek help when needed. Most likely, they had increased their medication consumption or had started using their prescribed pain medication more effective. However, the course of medication intake and improved empowerment were not investigated as an outcome in our study. Moreover, two of these previous studies also included patients with mild pain (NRS ≥ 2 [28] or ≥3 [29]), which resulted in a lower mean pain intensity at baseline. Therefore these studies were probably less likely to find a decrease in pain intensity.

Although we found no differences between groups on any QoL subscale, we found similar improvements in both groups regarding functional interference, psychosocial aspects, physical functioning, emotional functioning and overall QoL. Other studies on educational interventions with pain intensity and QoL as outcome measures also did not find QoL differences between the intervention and control-groups [16,17,28,30–35]. Moreover, pain is not always the most essential factor in patients' QoL [28]. In outpatients with painful bone metastases, depression, social functioning and physical functioning – and not pain – were found as the most important factors that predicted QoL [9].

Our study had several limitations. First, we could not blind patients and radiation oncologists to the intervention. To keep radiation oncologists as unbiased as possible, they were not informed directly about the PEP intervention. They provided routine care, consisting of patient intake, discussions on pain medication, treatment, and possible side effects. However, they also included the patients in the study, which possibly made them more aware of the benefits of additional pain education.

Second, we excluded 30 patients after randomization because their self-reported NRS was <5, while the radiation oncologist started radiation therapy for uncontrolled pain. A possible explanation for this discrepancy is that patients with uncontrolled pain started using analgesics while waiting for their referral to the radiation oncologist or between their visit and start of radiotherapy.

Third, studying the course of intake of pain medication including steroid intake would have given additional information on the

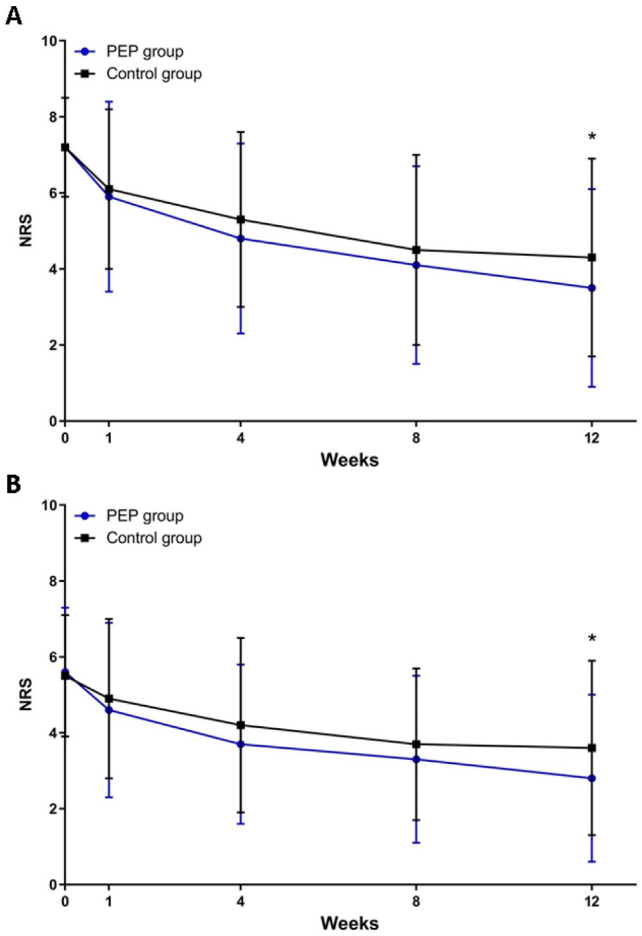

Fig. 3. Worst and average pain during follow-up (mean and standard deviation). NRS; 0–10 numeric rating scale, 0 = no pain, 10 = worst pain imaginable (A) Worst pain, * P =.0490 between groups at 12 weeks. (B) Average pain, * P =.0251 between groups at 12 weeks.

effect of PEP. The outcome that with PEP indeed patients start on medication, or are inclined to use higher doses, to bridge the three to four weeks necessary for the effect of the radiotherapy on pain to kick in, is very likely. Since we do not have these information, we could only report the baseline use of pain medication, which shows no differences between both groups.

A fourth limitation is that we lost a significant proportion (41%, 20% due to death) of the included patients during 12 weeks of follow-up, even though a life expectancy of ≥3 months and a WHO performance status 0–3 were inclusion criteria.

Our RCT has shown that the addition of nurse-led pain education for patients with painful bone metastases undergoing radiotherapy leads to controlled pain, defined as the worst pain intensity < 5, in more patients, and achieves controlled pain faster. Therefore, we strongly recommend that all patients who are referred to a radiotherapy department for the treatment of painful bone metastases should be offered a pain education program. Such a program can be easily included during a visit to the out-patient clinic, even when the intake and the radiotherapy are provided on the same day. Nurses who already provide patient information in the general practice or in the medical oncology department or dayclinic and see many patients with painful bone metastases can also be trained to integrate the PEP into their workflow. It is helpful if all involved clinicians inform patients about the beneficial effect of adequate pain management on their quality of life, and integrate such in their daily practice.

Table 3
Quality of Life measures during follow up.

	PEP group (n = 156) Mean (SD)	Control group (n = 152) Mean (SD)
Functional interference - EORTC QLQ-BM22		
Baseline	50.3 (22.1) n = 154	49.0 (22.5) n = 152
Week 1	58.9 (23.3) n = 133	57.9 (22.4) n = 117
Week 4	63.5 (21.3) n = 115	63.8 (20.4) n = 114
Week 8	67.0 (21.0) n = 114	65.0 (22.8) n = 92
Week 12	66.4 (23.1) n = 88	67.4 (22.2) n = 88
Physical functioning - EORTC QLQ-BM22		
Baseline	53.7 (26.0) n = 153	51.9 (25.2) n = 149
Week 1	56.6 (27.1) n = 129	53.8 (25.0) n = 120
Week 4	56.6 (24.7) n = 118	56.2 (23.4) n = 113
Week 8	58.5 (25.7) n = 117	55.4 (24.8) n = 93
Week 12	56.8 (28.0) n = 89	58.8 (25.9) n = 86
Psychosocial aspects - EORTC QLQ-BM22		
Baseline	46.3 (18.3) n = 154	44.3 (17.6) n = 152
Week 1	48.9 (16.4) n = 133	46.8 (18.1) n = 117
Week 4	50.6 (18.1) n = 116	46.4 (17.4) n = 116
Week 8	48.4 (17.7) n = 113	45.1 (18.8) n = 94
Week 12	48.8 (19.2) n = 90	47.5 (18.6) n = 89
Emotional functioning - EORTC QLQ-C15-PAL		
Baseline	72.1 (22.9) n = 154	71.0 (24.9) n = 150
Week 1	74.5 (21.3) n = 133	72.5 (26.1) n = 119
Week 4	75.9 (24.9) n = 120	75.3 (22.4) n = 116
Week 8	77.0 (21.8) n = 111	72.3 (25.8) n = 95
Week 12	75.5 (23.9) n = 90	73.4 (25.8) n = 88
Overall quality of life - EORTC QLQ-C15-PAL		
Baseline	58.9 (19.9) n = 151	57.5 (20.3) n = 149
Week 1	57.1 (21.1) n = 133	56.1 (19.4) n = 121
Week 4	62.0 (18.3) n = 119	59.1 (19.7) n = 116
Week 8	61.8 (19.2) n = 110	58.6 (22.3) n = 95
Week 12	61.6 (21.2) n = 88	61.4 (22.0) n = 88

Author Contributions

Conception and design: YvdL, AdG, AR.
Provision of study materials or patients: JIG, YvdL, VEMM, EJMdN, MAO, AdG, AR.
Collection and assembly of data: JIG, YvdL, AdG, AR.
Manuscript writing: All authors.
Final approval of manuscript: All authors.
Accountable for all aspects of the work: All authors.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten E, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage 2016;51:1090.
[2] Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. Pain 82:263-274, 1999.
[3] Rich SE, Chow R, Raman S, Liang Zeng K, Lutz S, Lam H, et al. Update of the systematic review of palliative radiation therapy fractionation for bone metastases. Radiother Oncol 2018;126:547–57.
[4] van der Linden YM, Lok JJ, Steenland E, Martijn H, van Houwelingen H, Marijnen CAM, et al. Single fraction radiotherapy is efficacious: a further

analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. Int J Radiat Oncol Biol Phys 2004;59:528–37.
[5] Lutz S, Balboni T, Jones J, Lo S, Petit J, Rich SE, et al. Palliative radiation therapy for bone metastases: Update of an ASTRO evidence-based guideline. Pract Radiat Oncol 2017;7:4–12.
[6] Chow E, van der Linden YM, Roos D, Hartsell WF, Hoskin P, Wu JS, et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol 2014;15:164–71.
[7] Sandblom G, Carlsson P, Sigsjo P, Varenhorst E. Pain and health-related quality of life in a geographically defined population of men with prostate cancer. Br J Cancer 2001;85:497–503.
[8] Strang P, Qvarner H. Cancer-related pain and its influence on quality of life. Anticancer Res 1990;10:109–12.
[9] Rustoen T, Moum T, Padilla G, Paul S, Miaskowski C. Predictors of quality of life in oncology outpatients with pain from bone metastasis. J Pain Symptom Manage 2005;30:234–42.
[10] Yates PM, Edwards HE, Nash RE, Walsh AM, Fentiman BJ, Skerman HM, et al. Barriers to effective cancer pain management: a survey of hospitalized cancer patients in Australia. J Pain Symptom Manage 2002;23:393.
[11] Oldenmenger WH, Sillevis Smitt PA, van Dooren S, Stoter G, van der Rijt CC. A systematic review on barriers hindering adequate cancer pain management and interventions to reduce them: A critical appraisal. Eur J Cancer 2009;45:1370–80.
[12] Cohen E, Botti M, Hanna B, Leach S, Boyd S, Robbins J. Pain beliefs and pain management of oncology patients. Cancer Nurs 2008;31:1.
[13] Bennett MI, Bagnall A, José CS. How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. Pain 2009;143:192–9.
[14] Oldenmenger WH, Geerling JI, Mostovaya I, Vissers KC, de Graeff A, Reyners AK, et al. A systematic review of the effectiveness of patient-based educational interventions to improve cancer-related pain. Cancer Treat Rev 2018;63:96–103.
[15] Koller A, Miaskowski C, De Geest S, Opitz O, Spichiger E. A systematic evaluation of content, structure, and efficacy of interventions to improve patients' self-management of cancer pain. J Pain Symptom Manage 2012;44:264–84.
[16] de Wit R, van Dam F, Zandbelt L, van Buuren A, van der Heijden K, Leenhouts G, et al. A pain education program for chronic cancer pain patients: follow-up results from a randomized controlled trial. Pain 1997;73:55–69.
[17] van der Peet EH, van den Beuken-van Everdingen MH, Patijn J, Schouten HC, van Kleef M, Courtens AM. Randomized clinical trial of an intensive nursing-based pain education program for cancer outpatients suffering from pain. Support Care Cancer 2009;17:1089–99.
[18] Dutch Society of Anesthesiology. Diagnostics and treatment of pain in patients with cancer, 2008.
[19] Delhaas E, Oldenmemger WH. Fabels en feiten over morfine en andere opioïden. 2017; Available at: https://www.pijnenkanker.nl/assets/uploads/2016/01/I-13-4887-Fabels-en-Feiten.pdf.
[20] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–38.
[21] Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, Bottomley A, et al. The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. Eur J Cancer 2006;42:55–64.
[22] Chow E, Hird A, Velikova G, Johnson C, Dewolf L, Bezjak A, et al. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for patients with bone metastases: the EORTC QLQ-BM22. Eur J Cancer 2009;45:1146–52.
[23] Steenland E, Leer JW, van Houwerlingen H, Post WJ, van den Hout WB, Kievit J, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiother Oncol 1999;5:101–9.
[24] Chow E, Hoskin P, Mitera G, Liang Zeng B, Lutz S, Roos D, et al. Update of the International Consensus on Palliative Radiotherapy Endpoints for future clinical trials in bone metastases. Int J Radiat Oncol Biol Phys 2012;82:1730–7.
[25] Dutch Society of Anesthesiology. Diagnostics and treatment of pain in patients with cancer. 2019. Available at http://www.pallialine.nl.
[26] Oldenmenger WH, Sillevis Smitt PA, van Montfort CA, de Raaf PJ, van der Rijt CC. A combined pain consultation and pain education program decreases average and current pain and decreases interference in daily life by pain in oncology outpatients: a randomized controlled trial. Pain 2011;152:2632–9.
[27] Kravitz RL, Tancredi DJ, Grennan T, Kalauokalani D, Street RL, Slee CK, et al. Cancer Health Empowerment for Living without Pain (Ca-HELP): effects of a tailored education and coaching intervention on pain and impairment. Pain 2011;152:1572–82.
[28] Thomas ML, Elliott JE, Rao SM, Fahey KF, Paul SM, Miaskowski C. A randomized, clinical trial of education or motivational-interviewing-based coaching compared to usual care to improve cancer pain management. Oncol Nurs Forum 2012;39:39–49.
[29] Koller A, Miaskowski C, De Geest S, Opitz O, Spichiger E. Results of a randomized controlled pilot study of a self-management intervention for cancer pain. Eur J Oncol Nurs 2013;17:284–91.
[30] Rustøen T, Valeberg B, Kolstad E, Wist E, Paul S, Miaskowski C. A Randomized clinical trial of the efficacy of a self-care intervention to improve cancer pain management. Cancer Nurs 2014;37:34–43.
[31] Williams JE, Peacock J, Gubbay AN, Kuo PY, Ellard R, Gupta R, et al. Routine screening for pain combined with a pain treatment protocol in head and neck cancer: a randomised controlled trial. Br J Anaesth 2015;115:621–8.
[32] Ling CC, Lui LY, So WK. Do educational interventions improve cancer patients' quality of life and reduce pain intensity? Quantitative systematic review. J Adv Nurs 2012;68:511–20.
[33] Anderson KO, Mendoza TR, Payne R, Valero V, Palos GP, Nazario A, et al. Pain education for underserved minority cancer patients: A randomized controlled trial. J Clin Oncol 2004;22:4918–25.
[34] Lovell MR, Forder PM, Stockler MR, Butow P, Briganti EM, Chye R, et al. A randomized controlled trial of a standardized educational intervention for patients with cancer pain. J Pain Symptom Manage 2010;40:49–59.
[35] Ward S, Donovan H, Gunnarsdottir S, Serlin RC, Shapiro GR, Hughes S. A randomized trial of a representational intervention to decrease cancer pain (RIDcancerPain). Health Psychol 2008;27:59–67.