Clinical Oncology 31 (2019) 391–398

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Possible Dose–Response Relationship in Palliative Radiotherapy for Non-bone Painful Lesions

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Received 18 September 2018; received in revised form 1 December 2018; accepted 25 February 2019

Abstract

Aims: Total radiation dose does not predict pain response in conventionally fractionated radiotherapy for bone metastases. By contrast, in radiotherapy for solid painful tumours other than bone metastases, it is unknown whether there is a dose–response relationship. We sought to determine whether a higher total radiation dose predicted a higher pain response rate in palliative radiotherapy for non-bone painful lesions.

Materials and methods: We carried out a secondary analysis of a prospective observational study. For patients scheduled for radiotherapy for painful tumours, Brief Pain Inventory data were collected at baseline and at 1, 2 and 3 months after the start of radiotherapy. The predictive value of total radiation dose was evaluated using the Fine–Gray model, in which death without a pain response was treated as a competing risk.

Results: Of the 203 patients with solid painful tumours, 78 (38%) had non-bone painful lesions. There were no significant differences in pain response rate, the rate of the predominance of non-index pain or reductions in pain interference scores between the patients with non-bone lesions and those with bone metastases. Multivariable analysis showed that total radiation dose was an independent significant predictor of pain response in patients with non-bone painful lesions. This result was not robust to sensitivity analysis with Cox regression analysis.

Conclusions: Higher total radiation dose seemed to be associated with a higher rate of pain response in patients with non-bone painful lesions. However, this finding was not robust to sensitivity analysis. Dose–response relationship should be investigated in clinical trials enrolling patients with these kinds of painful tumour.

Key words: Bone metastases; dose–response relationship; palliative radiotherapy; solid tumour

Introduction

Radiotherapy plays an important role in treating cancer pain [1,2], and much is known about the response rate [3], the duration of pain relief [4] and quality of life improvements [5,6] in patients with painful bone metastases. By contrast, far fewer data are available concerning palliative radiotherapy for solid painful tumours other than bone metastases. Although randomised controlled trials have shown that total radiation dose is not associated with pain response rate in conventionally fractionated radiotherapy for bone metastases [3], in patients with most painful tumours other than bone metastases, it is unknown whether there is a dose–response relationship. In a secondary analysis of our previous prospective observational study, we investigated whether there was a significant association between total radiation dose and pain response rate in patients with non-bone painful lesions. Another objective of the present study was to investigate whether there were any differences in pain response rate, the rate of the predominance of non-index pain or reductions in pain interference between patients with non-bone lesions and those with bone metastases.

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https://doi.org/10.1016/j.clon.2019.03.042
0936-6555/

Materials and Methods

Patients and Study Design

We carried out a secondary analysis of a previously published prospective observational study conducted at three medical centres [7]. In the primary study, there were 302 analysable patients (enrolled between July 2013 and September 2017) planned to receive radiotherapy for their painful tumours; we evaluated the characteristics of patients, tumours and pain to identify the predictors of pain response after radiotherapy for painful tumours [7]. Of these 302 patients, 203 patients treated with palliative radiotherapy for their solid painful tumours were analysed in the present study (Figure 1). Radiotherapy was defined as palliative if the primary purpose of the treatment was pain relief or if the radiation field did not cover all tumours identified by diagnostic imaging. Radiotherapy was carried out at the discretion of the treating radiation oncologists. The present study was approved by the participating centres' institutional review boards. Written informed consent was obtained from all enrolled patients in the primary study.

Evaluation

The patients were evaluated as previously reported [7]. Briefly, we used the Brief Pain Inventory (BPI) short form to evaluate the intensity of pain and the interference of pain in the patient's life using an 11-point scale (0–10). Higher scores mean greater pain intensity and greater pain interference [8]. Patients reported their worst pain (in terms of the index pain caused by the irradiated tumour) in the previous 3 days. The BPI assesses pain interference in seven subscales: general activity, mood, walking ability, normal work, relationships with other people, sleep and enjoyment of life. We collected the BPI and analgesic data at baseline and at 1, 2 and 3 months (±7 days) after the start of radiotherapy. The pain response was assessed using the International Consensus Endpoint for clinical trials in bone metastases [9]. Patients who received radiotherapy for painful tumours were categorised as responders or non-responders; responders included patients who experienced complete and partial responses. A complete response was defined as an index pain score of 0 with no increase in the daily oral morphine equivalent dose (OMED) [9]. A partial response was defined as a reduction in pain score of ≥2 without an increase in OMED or a reduction in analgesic use of ≥25% without an increase in the pain score. Pain progression was defined as an increase in the index pain score of ≥2 without reduced OMED or an increase of ≥25% in OMED without a decrease in the pain score. An indeterminate response was defined as any response that was not captured by the complete response, partial response or pain progression definitions.

In addition to the index pain (pain caused by the irradiated tumour), non-index pain was assessed [10]. At baseline and at follow-ups, the treating radiation oncologists prospectively evaluated whether the patients had pain other than the index pain and, for the patients with this pain, its intensity (the worst pain in the previous 3 days) and origin were recorded. Non-index pain was classified as pain of a malignant (tumour-related) origin, unknown origin, benign origin or as treatment-related. Patients were diagnosed with a predominance of other pain (POP) if non-index pain of a malignant or unknown origin was present and had a greater 'worst pain' score than the index pain at follow-up [10].

Statistical Analysis

Patients' characteristics were analysed using the Mann–Whitney U tests for continuous variables and Fisher exact tests for categorical variables. Eastern Cooperative Oncology Group (ECOG) performance status (≤1 versus >1) and worst pain score at baseline (≤7 versus >7) were treated as binary variables, and age and total radiation dose were treated as continuous variables. Pain interference score changes from baseline to follow-up were analysed using the Mann–Whitney U tests. Pain response rates and the rates of patients with POP were compared between the patients with non-bone painful lesions and those with bone metastases using Fisher exact tests.

We carried out univariable and multivariable analyses to assess the predictors of pain response using the method of Fine and Gray [11]. In this survival analysis, death without a pain response was treated as a competing risk. In evaluating whether there is a relationship between total radiation dose and pain response, seven covariates were selected to adjust for any confounding effects: age, sex, ECOG performance status, worst pain score at baseline, presence of a neuropathic component of the index pain, opioid analgesic use at baseline and adjuvant analgesic use at baseline. The variance inflation factor was used to assess multicollinearity between independent variables. As a sensitivity analysis of our analysis with the method of Fine and Gray, a Cox regression analysis was carried out [12,13]. In the Cox regression analysis, patients who died without experiencing a pain response were considered censored. The linearity assumption of continuous variables was checked using the plot of the Martingale residuals. The proportionality assumption of proportional hazards analysis was checked using Schoenfeld's residuals. All covariates with a P value < 0.20 at univariable analysis were included in the multivariable analysis.

All tests were two-tailed and a P value < 0.05 was considered significant. Statistical analyses were carried out with SPSS software version 24 (IBM SPSS, Armonk, NY, USA) and R version 3.0.2.

Results

Patients

Of the 203 patients with solid painful tumours, 78 (38%) had non-bone painful lesions (Table 1); the irradiated tumours ($n = 78$) were primary tumour lesion ($n = 26$), lymph

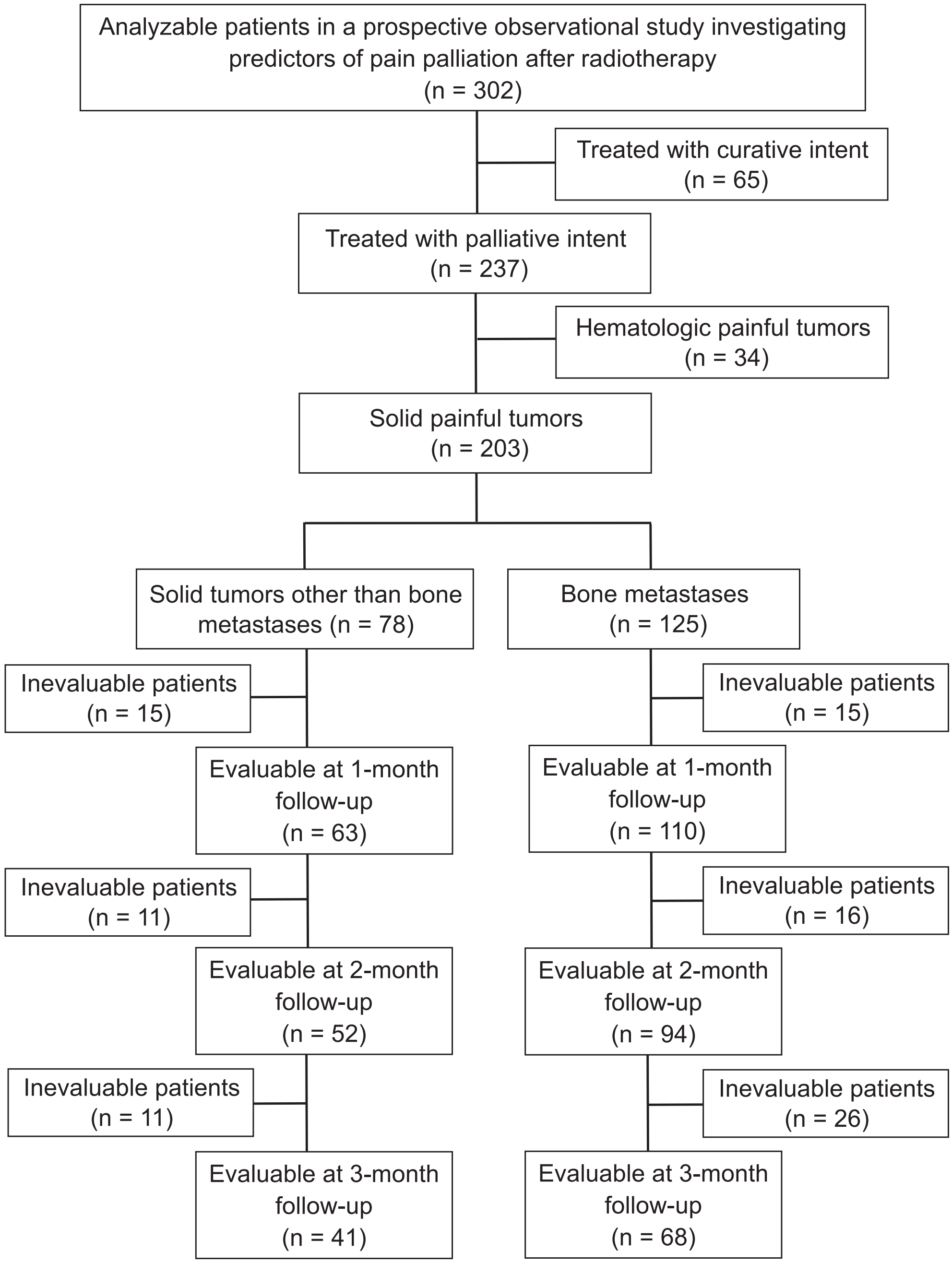

Fig 1. Flow diagram of the study cohort.

node metastasis ($n = 25$), haematogenous metastasis other than bone metastasis ($n = 6$), pleural dissemination ($n = 11$) and other ($n = 10$). There were more female patients with non-bone lesions than with bone metastases (Table 1). The patients with non-bone painful lesions were treated with a higher total radiation dose than those with bone metastases (Table 1).

Pain Response

At baseline and at 1, 2 and 3 months of follow-up, the mean worst pain scores were 6.7, 3.1, 2.3 and 2.2 in the patients with non-bone painful lesions, respectively (Figure 2). These values were 7.1, 3.9, 3.2 and 2.5 in patients with bone metastases, respectively.

In total, 105 (52%) of the 203 patients experienced a pain response within 3 months after the start of radiotherapy. For the patients with non-bone painful lesions and those with bone metastases, the pain response rates for evaluable patients were 52 and 45% at 1 month ($P = 0.35$), 54 and 52% at 2 months ($P = 0.86$) and 51 and 51% at 3 months of follow-up ($P = 1.00$), respectively (Table 2). The intention-to-treat pain response rates for all 78 patients with non-bone painful lesions and 125 patients with bone metastases were 42 and 39% at 1 month, 36 and 39% at 2 months and 27 and 28% at 3 months of follow-up, respectively.

Table 1
Baseline patient characteristics

Characteristic	Non-bone painful lesions ($n = 78$)		Bone metastases ($n = 125$)		P value
	No.	%	No.	%	
Age, years					0.068
Median	66		68		
Range	21–87		35–91		
Gender					0.018
Female	40	51	42	34	
Male	38	49	83	66	
ECOG performance status					0.24
0	16	21	13	10	
1	34	44	56	45	
2	21	27	39	31	
3, 4	7	9	17	14	
Primary sites of the tumours					
Lung	20	26	49	39	
Gastrointestinal system	15	19	35	28	
Gynaecological system	14	18	11	9	
Head and neck	9	12	6	5	
Urogenital system	5	6	10	8	
Breast	5	6	9	7	
Skin	4	5	0	0	
Other	6	8	5	4	
Worst pain score at baseline					0.11
1–2	4	5	2	2	
3–4	15	19	16	13	
5–7	27	35	41	33	
8–10	32	41	66	53	
Neuropathic component of index pain					0.76
No	54	69	83	66	
Yes	24	31	42	34	
Non-index pain of malignant or unknown origin at baseline					0.42
No	69	88	104	83	
Yes	9	12	21	17	
Opioid analgesic use at baseline					0.47
No	33	42	60	48	
Yes	45	58	65	52	
Adjuvant analgesic use at baseline					1.00
No	50	64	79	63	
Yes	28	36	46	37	
Total radiation dose, Gy					<0.001
Median	32.5		30		
Range	6–60		8–50		
≤10	5	6	33	26	
10–20	5	6	19	15	
20–30	29	37	54	43	
>30	39	50	19	15	

ECOG, Eastern Cooperative Oncology Group.

Predominance of Other Pain

For the patients with non-bone painful lesions and those with bone metastases, the rates of POP in patients were 10% (6/63 patients) and 5% (6/110 patients) at 1 month ($P = 0.36$), 12% (6/52 patients) and 11% (10/94 patients) at 2 months ($P = 1.00$) and 12% (5/41 patients) and 15% (10/68 patients) at 3 months of follow-up, respectively ($P = 0.78$).

Brief Pain Inventory Pain Interference Scores

The mean pain interference scores at baseline and at the 1, 2 and 3 months of follow-up are shown in Figure 2. For the patients with non-bone painful lesions and those with bone metastases, the mean differences in scores at 2 months of follow-up (i.e. follow-up minus baseline) were −2.3 and −3.0 for general activity ($P = 0.45$), −2.5 and −2.6 for mood ($P = 0.96$), −2.2 and −2.5 for walking

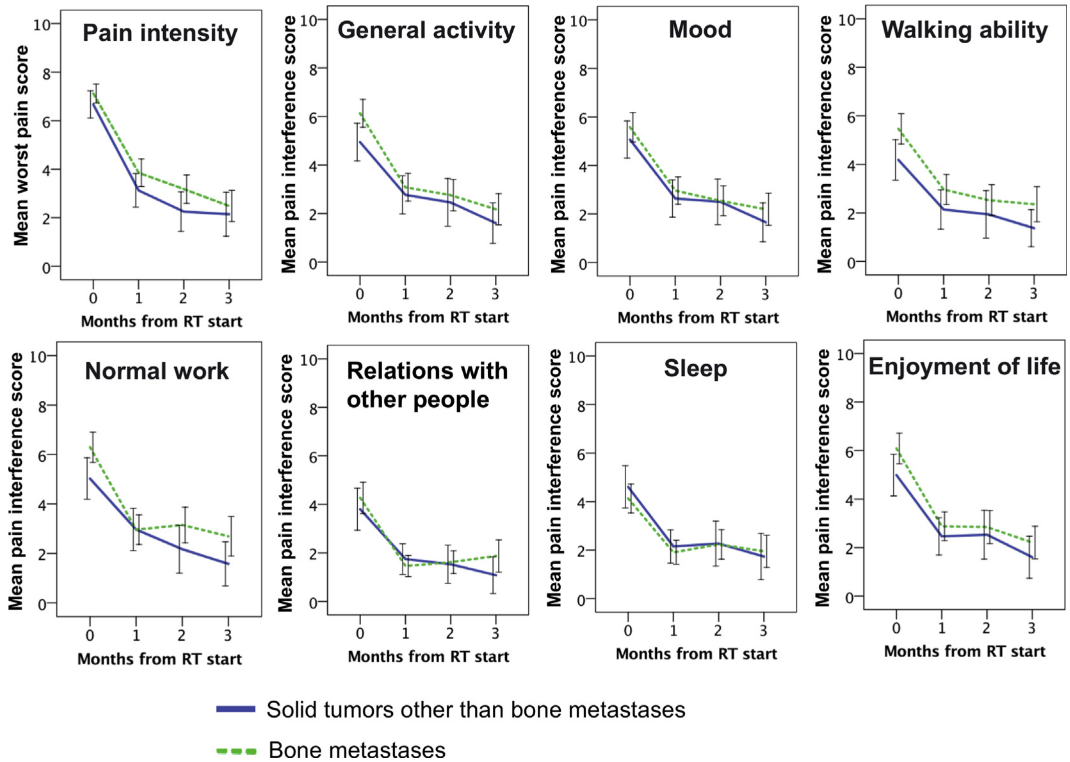

Fig 2. Pain intensity and pain interference at baseline and at 1, 2 and 3 months of follow-up. The error bars indicate the 95% confidence intervals. RT, radiotherapy.

ability ($P = 0.94$), −2.5 and −2.7 for normal work ($P = 0.89$), −1.7 and −2.6 for relationships with other people ($P = 0.22$), −2.2 and −1.4 for sleep ($P = 0.43$) and −2.0 and −2.8 for enjoyment of life ($P = 0.42$), respectively.

Analysis of Dose–Response Relationship

There were no missing values in the eight independent variables. The variance inflation factors ranged from 1.02 to 1.19, which indicated that there was no multicollinearity

Table 2
Pain response to radiotherapy

Response	Non-bone painful lesions		Bone metastases		*P* value*
	No.	%	No.	%	
1 month of follow-up	$n = 63$		$n = 110$		0.35
Complete response	12	19	16	15	
Partial response	21	33	33	30	
Pain progression	9	14	14	13	
Indeterminate response	21	33	47	43	
2 months of follow-up	$n = 52$		$n = 94$		0.86
Complete response	18	35	14	15	
Partial response	10	19	35	37	
Pain progression	2	4	8	9	
Indeterminate response	22	42	37	39	
3 months of follow-up	$n = 41$		$n = 68$		1.00
Complete response	12	29	17	25	
Partial response	9	22	18	26	
Pain progression	4	10	7	10	
Indeterminate response	16	39	26	38	

The pain response rate was calculated for evaluable patients.
* Fisher exact tests were used to compare the pain response (complete response + partial response) rates between the two groups.

problem for the independent variables. Based on the inspection of the plot of the Martingale residuals, the linearity assumption was not violated for age and total radiation dose. The proportionality assumption of proportional hazards analysis was not violated based on Schoenfeld's residuals. In total, 29 (14%) of the 203 patients died without experiencing a pain response. For these 29 patients, the median time to death from the start of radiotherapy was 29 days (range 12–85 days). Table 3 shows the analysis to evaluate the predictors of pain response using the method of Fine and Gray in the 78 patients with non-bone painful lesions. Multivariable analysis showed that female gender, the presence of a neuropathic component of the index pain and total radiation dose were independent significant predictors of pain response (Table 3). A higher total radiation dose was associated with a higher rate of pain response. Cox regression analysis performed as a sensitivity analysis determined that the total radiation dose was not a significant predictor of pain response at both univariable and multivariable analyses (Table 4).

For the 125 patients with bone metastases we also carried out univariable and multivariable analyses to assess the predictors of pain response using the method of Fine and Gray. At univariable analysis investigating the same eight independent variables as in the analysis of the patients with non-bone lesions, ECOG performance status (hazard ratio 1.61; 95% confidence interval 0.98–2.62; $P = 0.058$) and total radiation dose (hazard ratio 1.02; 95% confidence interval 1.00–1.04; $P = 0.075$) showed $P < 0.20$ and were then included in the multivariable analysis. Multivariable analysis showed that ECOG performance status >1 was a significant predictor of pain response (hazard ratio 1.69; 95% confidence interval 1.02–2.81; $P = 0.044$), whereas total radiation dose was not (hazard ratio 1.02; 95% confidence interval 1.00–1.04; $P = 0.052$).

Discussion

We found that higher total radiation dose seemed to be associated with a higher rate of pain response in patients with non-bone painful lesions. However, this finding was not robust to sensitivity analysis using Cox regression analysis. In addition, from the results of the multivariable analyses to assess the predictive value of the total radiation dose on pain response in patients with bone metastases (marginally significant; $P = 0.052$), we suspect the presence of unadjusted confounding factors; for bone metastases, there is no dose–response relationship with conventional radiotherapy [3]. A dose–response relationship in patients with non-bone painful lesions should be investigated in randomised controlled trials.

A few randomised controlled trials have investigated whether there is a dose–response relationship in radiotherapy for non-bone painful lesions. In a systematic review of palliative radiotherapy for patients with thoracic symptoms from non-small cell lung cancer, there was no strong evidence that any regimen provides greater palliation [14]; two randomised controlled trials showed that patients

Table 3
The Fine and Gray method to assess the relationship between total radiation dose and pain response in patients with non-bone painful lesions ($n = 78$)

Variable	Univariable analysis*			Multivariable analysis*		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years (continuous)	1.01	0.99–1.04	0.62			
Gender						
Female	1.00 (reference)			1.00 (reference)		
Male	0.47	0.24–0.89	0.021	0.44	0.22–0.87	0.019
ECOG performance status						
0,1	1.00 (reference)					
2–4	1.33	0.71–2.47	0.37			
Worst pain score at baseline						
0–7	1.00 (reference)					
8–10	1.13	0.60–2.12	0.70			
Neuropathic component of index pain						
No	1.00 (reference)			1.00 (reference)		
Yes	1.85	0.98–3.49	0.057	2.94	1.59–5.44	<0.001
Opioid analgesic use at baseline						
No	1.00 (Reference)					
Yes	0.95	0.53–1.70	0.86			
Adjuvant analgesic use at baseline						
No	1.00 (reference)					
Yes	1.00	0.53–1.89	0.99			
Total radiation dose, Gy (continuous)	1.04	1.01–1.07	0.003	1.04	1.01–1.07	0.006

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.
Covariates with a *P* value < 0.20 at univariable analysis were included in the multivariable analysis to adjust for any confounding effects.
* Death without a pain response was treated as a competing risk.

Table 4
Cox regression analysis to assess the relationship between total radiation dose and pain response in patients with non-bone painful lesions ($n = 78$)

Variable	Univariable analysis*			Multivariable analysis*		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years (continuous)	1.02	0.99–1.04	0.14	1.01	0.99–1.04	0.26
Gender						
Female	1.00 (reference)			1.00 (reference)		
Male	0.62	0.32–1.19	0.15	0.51	0.25–1.02	0.056
ECOG performance status						
0,1	1.00 (reference)			1.00 (reference)		
2–4	2.43	1.25–4.73	0.009	2.02	1.00–4.07	0.049
Worst pain score at baseline						
0–7	1.00 (reference)					
8–10	1.11	0.58–2.11	0.75			
Neuropathic component of index pain						
No	1.00 (reference)			1.00 (reference)		
Yes	2.14	1.12–4.08	0.021	2.67	1.31–5.46	0.007
Opioid analgesic use at baseline						
No	1.00 (Reference)					
Yes	1.13	0.60–2.11	0.70			
Adjuvant analgesic use at baseline						
No	1.00 (reference)					
Yes	0.99	0.52–1.90	0.97			
Total radiation dose, Gy (continuous)	1.02	0.99–1.05	0.23	1.02	0.99–1.06	0.21

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.
Covariates with a P value < 0.20 at univariable analysis were included in the multivariable analysis to adjust for any confounding effects.
* Patients who died without experiencing a pain response were considered censored.

treated with multifractional regimens showed a significant improvement in chest pain compared with those treated with a single fraction [15,16]. A prospective randomised study of palliative radiotherapy of multiple myeloma showed that there were no differences in analgesic response between the patients treated with 3 Gy × 10 fractions and those treated with 8 Gy × 1 fraction [17]. Quality of life improved after radiotherapy only in patients treated with the multifractional regimen, and the authors recommended that higher doses should be used to achieve a better quality of life [17]. Future trials on radiotherapy for non-bone painful lesions are warranted.

Another finding of the present study was that there were no significant differences in pain response rate, the rate of the predominance of non-index pain or reductions in pain interference scores between the patients with non-bone painful lesions and those with bone metastases. For patients with non-bone painful lesions, palliative radiotherapy may be beneficial, as well as for patients with painful bone metastases.

Our pain response rates of 45–54% for evaluable patients and 27–42% for intention-to-treat patients were comparable with response rates of 55% for evaluable patients and 29% for intention-to-treat patients that were reported in a recent systematic review of palliative radiotherapy for painful bone metastases in non-randomised studies [18]. In non-randomised studies, lower pain response rates have been reported than in randomised studies [18].

We found that a neuropathic component of the index pain was a significant predictor of pain response for non-bone lesions in multivariable analyses (Tables 3 and 4). These findings are in line with those in our original study [7]. The presence or absence of a neuropathic component might be worth evaluating at baseline to predict pain response in patients receiving palliative radiotherapy.

In the present study, the patients with non-bone painful lesions tended to be treated with a higher total radiation dose than those with bone metastases. This may be because the treating radiation oncologists were not certain whether low-dose radiotherapy (e.g. 8 Gy in one fraction or 20 Gy in five fractions) was effective for non-bone painful lesions and tended to prescribe a higher total radiation dose. Limited data are available for these kinds of painful tumour, whereas for painful bone metastases, the effectiveness of low-dose radiotherapy has been shown in many studies [3,19].

The present study had limitations. First, the sample size was small and we could not adjust for potential confounding factors sufficiently. Second, the present study included heterogeneous patients and the actual number of patients with specific diseases was relatively small. Again, our sample size did not allow for analyses of specific diseases. The present study can only be a starting point for future studies investigating specific diseases. Third, factors that may have influenced the radiation oncologists' choices of treatment could not be analysed. In the original observational study, radiotherapy was carried out at the discretion of the treating radiation oncologist. We included patients with heterogeneous tumours who might have had miscellaneous symptoms and problems caused by the irradiated tumours, such as bleeding or obstruction. The treating radiation oncologists may have decided the dose fractionation based on the symptoms and problems caused by the tumours, tumour location and histology, and patient performance status. These factors might have confounded the outcomes. However, the radiation oncologists' treatment objectives or reasons for choices of dose fractionations were not recorded and could not be analysed.

Despite the limitations, the present study suggests that there may be a dose–response relationship in the radiotherapy for non-bone painful lesions. Judicious use of low-dose radiotherapy may be reasonable for palliation of pain from these kinds of painful tumour until our findings are tested in future clinical trials. Patients with non-bone painful lesions seem to have derived similar benefits from radiotherapy as patients with painful bone metastases. For tumour-related pain, palliative radiotherapy should be considered, irrespective of whether the painful tumour is a bone metastasis or not.

Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.03.042.

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