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Quality of life improvement in patients with bone metastases undergoing palliative radiotherapy

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ABSTRACT

Background: The aim of the study was to analyze the impact of palliative radiotherapy on quality of life (QoL) in patients with symptomatic bone metastases.

Materials and methods: We present the results from a prospective multicentric study including 128 patients who provided pre- and post-radiotherapy (one month after treatment) brief pain inventory (BPI) assessments. Worst pain was recorded using the BPI (range: 0–10). Pain response was described according to the International Bone Metastases Consensus on palliative radiation. Regarding QoL, for each pre- and post-radiation BPI-questionnaire, scores from the interference domains were summed and averaged to obtain an overall interference score.

Results: There was a significant correlation between radiation treatment response and improvement in all functional interference domains except sleeping. Patients > 75 years old presented a significantly higher improvement in general activity, mood and relationships with others compared to patients ≤ 75 years old. Patients presenting a baseline pain score ≥ 8 showed a higher improvement in the general activity item ($p = 0.049$). There was no statistically significant association between pre-treatment ECOG, chemotherapy, primary tumor location and radiation schedule with any of the functional interference items.

Conclusions: Patients who report pain relief after palliative radiotherapy also present a better quality of life including physical and psychosocial aspects.

Key words: pain; palliative radiotherapy; bone metastases; quality of life

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Introduction

One of the most frequent symptoms of bone metastases is pain, occurring in approximately 70% of patients [1]. As a result of bone pain, patients frequently have increasing difficulty regarding activities of daily living, showing significant suffering, and decreasing quality of life (QoL).

Radiotherapy (RT) is considered an effective therapy for cancer patients with symptomatic bone metastases. Numerous studies have reported that approximately 50-80% of patients receiving palliative RT for symptomatic bone metastases experience pain relief at some degree [2], and around one third of them will present complete pain response [3].

However, although pain relief is a proven benefit of RT, it does not necessarily indicate a subsequent QoL improvement [4]. Indeed, there are few studies that report QoL results. Moreover, there are contradictory results, as some studies report that there is an improvement in the QoL in those patients who respond positively to RT treatment [5–9] while others report that RT does not equally improve the QoL in all domains [10–12].

In addition, limited information has been reported regarding the influence of pre-treatment clinical parameters such as age, pre-treatment pain intensity score, tumor location or performance status on the QoL after treatment.

Therefore, the objective of the present study was to address through Brief Pain Inventory (BPI) whether there is an improvement in the QoL of patients with bone metastasis who respond to palliative RT. Additionally, we have evaluated whether any clinical or treatment-related variables used in daily clinical practice can influence the QoL reported by patients after treatment.

Materials and methods

This is a prospective multicentre observational study. Patients with painful bone metastasis referred to palliative RT were eligible for the present study. The inclusion criteria were as follows: ≥ 18 years of age, radiological evidence of symptomatic bone metastasis, capability to complete thee BPI questionnaire and the daily analgesic intake diary. Written informed consent was obtained from each patient. This study was approved by the Institutional Ethics Committee of each participating centre.

Indeed, the present study is a secondary QoL assessment of the population originally recruited for the "Flare study" for which the primary objective was to address the incidence of the flare effect in patients with bone metastasis undergoing palliative RT. The study protocol details have been published elsewhere [13].

The treatment was administered with 3D conformal RT. Radiation schedules consisted of a single treatment of 8 Gy or a multi-fraction approach (20 Gy administered in four or five daily sessions). The treatment fractionation was selected by the treating physician.

The prospectively collected QoL data of 204 patients with breast, prostate, and lung cancer and other tumor locations within the Flare study were analysed [13]. These data included functional QoL domain scores to determine whether palliative RT improved QoL in patients with symptomatic bone metastases receiving palliative RT. Moreover, potential relationships between clinical and treatment variables (age, gender, tumor location, treatment response, radiation schedule, primary tumor location, use of chemotherapy or use of bisphosphonates) and QoL after receiving RT were explored.

Patient clinical evaluation

Patient baseline evaluation before RT included a full clinical history including a physical examination. All patients were encouraged to fulfil the BPI questionnaire to estimate pre-treatment pain intensity, including an 11-point numeric scale ranging from 0 (no pain) to 10 (the worst possible pain). The BPI also included several QoL related questions [14, 15]. The total quantity of analgesics needed by each patient (in the last 24 hours) was also recorded.

One month after the end of radiation treatment, a follow-up visit was arranged at each participating hospital where the BPI was again administered to evaluate pain response, analgesics intake and QoL.

Analysis of the pain response

We evaluated the pain response of patients by calculating the difference between scores obtained in the baseline evaluation and four weeks after treatment. Pain response was described as complete response, partial response, stable disease or progression according to the International Bone Metastases Consensus on palliative RT [16]. Pain response was

defined as a decrease in the baseline pain score by at least two points (without increasing analgesic intake), or analgesic decrease without increasing pain score. Full data regarding pain response and clinical parameters associated with a better response have been previously published elsewhere [13, 17].

Quality of life analysis

The BPI contains a pain scale, and QoL-related questions aiming to include items that report the "sensory" dimension of pain intensity and the reactive dimension of pain (interference with daily functions) [15]. Interference in the 7 items - general activity, normal work (inside or outside of the home), mood, relationships with others, walking capability, sleeping quality, and life enjoyment was scored between 0 (does not interfere at all) and 10 (completely interferes) for all items. The BPI questionnaire was self-administered at the baseline evaluation (before RT) and one month after RT (during the follow-up appointment) to assess the QoL improvement.

Statistical analysis

Continuous variables were expressed as the mean and standard deviation (or median and range in case of quantitative variables). On the other hand, categorical variables are described as frequencies and percentages. For each pre- and post-radiation BPI-questionnaire, scores from the BPI interference domains were summed and averaged to obtain an overall interference score. Changes in mean functional interference scores (pre- and post-treatment) were compared with the non-parametric Wilcoxon signed ranks test. To analyze possible relationships between changes in functional interference and each variable (age, gender, primary tumor location, treatment response, radiation schedule, use of chemotherapy, use of bisphosphonates) the non-parametric Mann Whitney U test was used with dichotomous variables (two categories), whereas non-parametric Kruskal Wallis test was used with categorical variables (> 2 categories). Subsequently, variables with a $p < 0.2$ in the univariate analysis were included in the multivariate lineal regression analysis (using a non-automatic stepwise procedure), to assess whether they were statistically significant independent predictors (p-value < 0.05) and the corresponding confidence intervals (CIs). Statistical significance was defined by a $p < 0.05$. Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 23.0)

Results

Between June 2010 and June 2014, a total of 204 patients were recruited from 10 participating hospitals [13].One month after RT, 128 patients returned the BPI questionnaires and were therefore considered eligible to evaluate pain response and QoL. The reasons for incomplete data are as follows: 25 patients experienced a deterioration in their performance status, 20 patients did not complete the pain diary, there were 16 unknown reasons for incomplete data and 15 patients requested removal from the study. The median age was 66 years (38–89) and 81 patients (63.3%) were male. The characteristics of the population are detailed in Table 1 and Supplementary File — Table 2.

Table 1. Characteristics of the patient population

Variable	No. patients (%)
Age, median (range)	66 years (38–89)
Age groups	
≤ 65 years	56 (43.8)
66–75 years	46 (35.9)
> 75 years	26 (20.3)
Sex	
Male	81 (63.3)
Female	47 (36.7)
ECOG Performance Status	
0	23 (18)
1	61 (47.7)
2	39 (30.4)
3	5 (3.9)
Worst pain at baseline, before radiotherapy	
≤ 4	14 (10.9)
5–7	42 (32.8)
≥ 8	72 (56.3)
Visceral metastasis	
Yes	54 (42.2)
No	74 (57.8)
Tumor location	
Lung	42 (32.8)
Prostate	22 (17.2)
Breast	19 (14.8)
Other	45 (35.2)

→

Table 1. Characteristics of the patient population

Variable	No. patients (%)
Systemic chemotherapy (within 4 weeks previous to radiotherapy)	
Yes	56 (43.7)
No	72 (56.3)
Bisphosphonates (within 4 weeks previous to radiotherapy)	
Yes	35 (27.3)
No	93 (72.7)
Location of the bone metastasis	
Axial (pelvis and spine)	76 (59.4)
Lower extremity	21 (16.4)
Upper extremity	13 (10.2)
Others	18 (14)
Treatment schedule groups	
Single fraction 8 Gy	37 (22.4)
Multiple fraction	91 (77.6)
20 Gy/5 fractions	79 (86.8)
20 Gy/4 fractions	12 (13.2)
Treatment response to radiotherapy	
Complete response (CR)	15 (11.7)
Partial response (PR)	64 (50.0)
Stable disease (SD)	35 (27.4)
Progression (P)	14 (10.9)

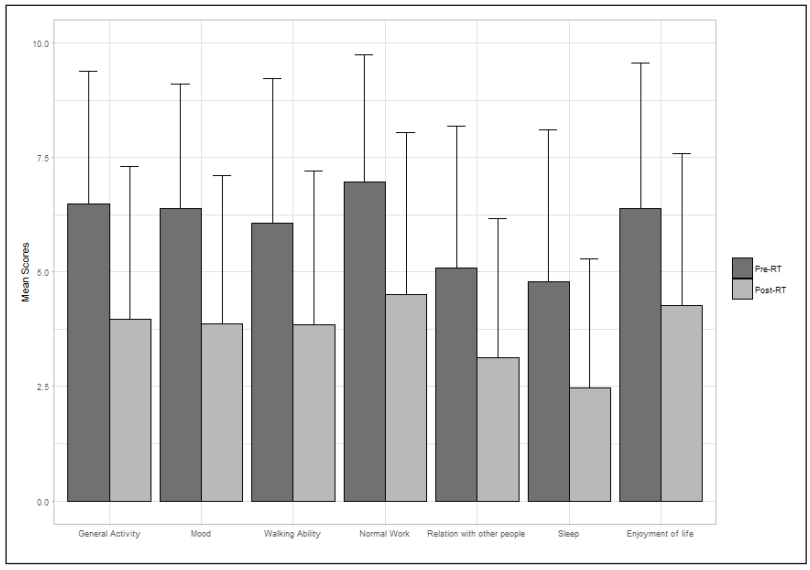
ECOG — Eastern Cooperative Oncology Group

There was a treatment overall response (OR) including partial and complete responses in 79 out of 128 patients (61.7%) whereas 35/128 patients (27.4%) and 14/128 patients (10.9%) presented stable response and pain progression, respectively. Full data regarding pain response and clinical parameters associated with a better response have been previously published elsewhere [17].

Baseline means functional interference scores, before and after radiation treatment was administered, are shown in Figure 1. Regarding the whole population of the study, a significant improvement for all seven functional interference items was seen one month after RT (Fig. 1).

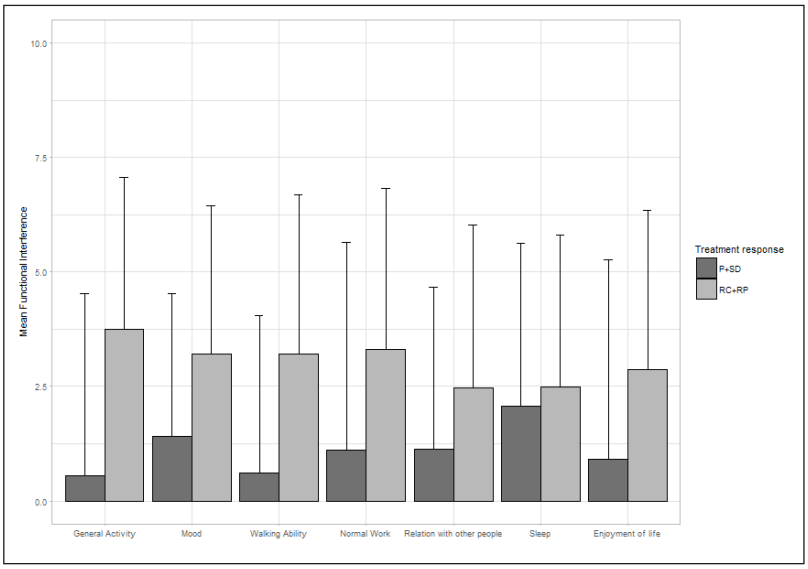
According to treatment response, we found that patients presenting a favourable pain response one month after RT also associated a statistically significant QoL improvement in all the functional interference items, except sleeping (Fig. 2).

Moreover, patients > 75 years old presented a significant higher improvement in general activity, mood and relationships with others compared to patients ≤ 75 years of age (see Fig. 3 and Tab. 3). Regarding gender, we found that females presented better improvement in enjoyment of life compared to males (p = 0.002) although there was no other



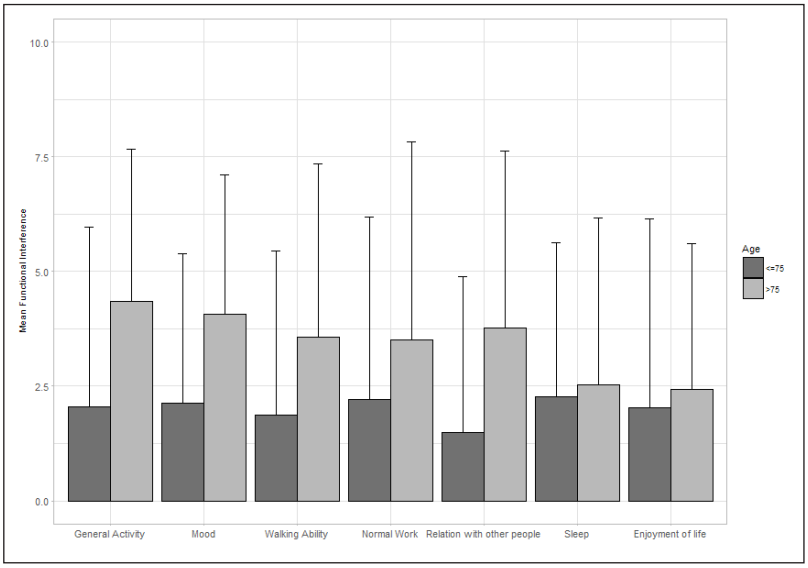
	General activity	Mood	Walking ability	Normal work	Relations with other people	Sleep	Enjoyment of life
Average change in score post-treatment	2.52	2.52	2.21	2.47	1.95	2.32	2.12
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Figure 1. Global improvement of quality of life for the whole population



	General activity	Mood	Walking ability	Normal work	Relations with other people	Sleep	Enjoyment of life
Treatment response							
P + SD	0.551	1.41	0.61	1.10	1.12	2.06	0.92
CR + PR	3.75	3.21	3.20	3.32	2.47	2.48	2.86
p-value	**< 0.001**	**0.004**	**< 0.001**	**0.003**	**0.018**	0.356	**0.006**

Figure 2. Mean functional interference improvement in different functional interference items according to treatment response one month after radiotherapy. P — progression; SD — stable disease; CR — complete response; PR — partial response



	General activity	Mood	Walking ability	Normal work	Relations with other people	Sleep	Enjoyment of life
Age							
≤ 75	2.06	2.12	1.86	2.21	1.49	2.26	2.04
> 75	4.34	4.08	3.58	3.50	3.77	2.538	2.42
p-value	**0.008**	**0.008**	0.092	0.216	**0.008**	0.691	0.955

Figure 3. Mean functional interference scores improvement according to age

Table 2. Evaluable and non-evaluable patients regarding tumor location

Primary cancer site	Evaluable patients (n = 128)	Non-evaluable patients (n = 76)
Lung	42 (32.8%)	21 (27.6 %)
Prostate	22 (17.2 %)	15 (19.8 %)
Breast	19 (14.8 %)	5 (6.6 %)
Others	45 (35.2 %)	35 (46 %)

significant difference regarding any other functional interference item.

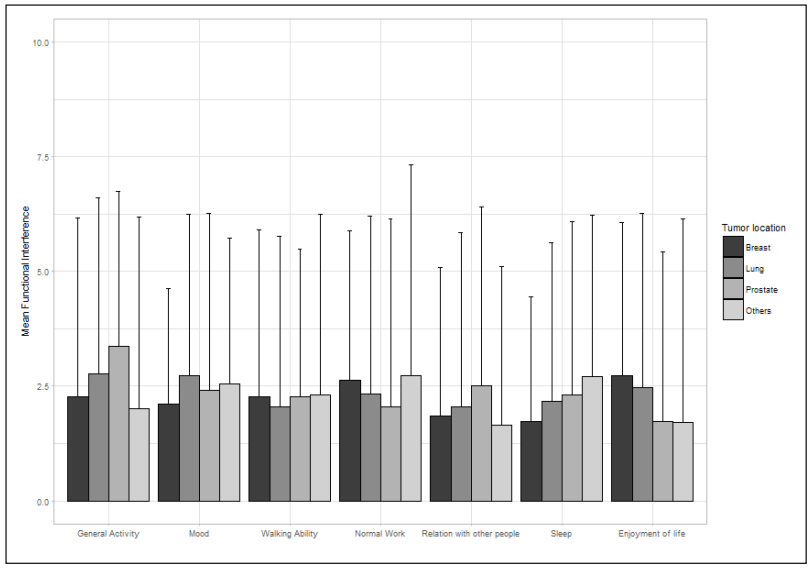
Moreover, patients presenting a baseline pain score ≥8 showed a higher improvement in the general activity item (p = 0.049) although no other differences were found according to any other functional interference items (Tab. 3).

According to the multivariate analysis, treatment response to RT was an independent predictor of improvement in general activity (p < 0.001), mood (p = 0.009), walking ability (p < 0.001), normal work (p = 0.002) and enjoyment of life (p < 0.011). Moreover, being a patient < 75 years was also an independent predictor of improvement in general activity (p = 0.048), mood (p = 0.026) and relations with other people (p = 0.004). Finally, gender (woman) also was as an independent factor regarding enjoyment of life improvement. All these variables are considered significant independent predictors. The results of multivariate analysis are shown in full in Supplementary File — Table 4.

Finally, we did not find any statistically significant association between pretreatment ECOG, chemotherapy, primary tumor location (Fig. 4) and radiation schedule with any of the functional interference items (Tab. 3).

Discussion

Pain relief and reduction of analgesics are often the main goals of palliation. However, improvement in functional capacity of the patients should also be considered one of the most crucial aspects in the context of palliative RT. The response to RT and pain relief is expected to be associated with an improvement in QoL. According to our



	General activity	Mood	Walking ability	Normal work	Relations with other people	Sleep	Enjoyment of life
Tumor location							
Breast	2.26	2.11	2.26	2.63	1.84	1.74	2.74
Lung	2.76	2.74	2.05	2.33	2.05	2.17	2.48
Prostate	3.36	2.41	2.27	2.05	2.50	2.32	1.73
Others	2.00	2.56	2.31	2.73	1.64	2.71	1.71
p-value	0.766	0.949	0.823	0.696	0.924	0.736	0.609

Figure 4. Mean functional interference scores according to primary tumor location

Table 3. Changes in mean functional interference scores pre- and post-treatment according to different clinical variables

	General Activity	Mood	Walking ability	Normal Work*	Relations with other people	Sleep	Enjoyment of life
Gender							
Male	2.28 ± 3.98	2.32 ± 3.37	1.94 ± 3.62	2.11 ± 4.31	1.73 ± 3.78	2.28 ± 3.58	1.38 ± 4.13
Female	2.94 ± 3.75	2.87 ± 3.15	2.68 ± 3.74	3.09 ± 3.56	2.34 ± 3.26	2.00 ± 3.13	3.38 ± 3.23
p-value	0.342	0.337	0.211	0.266	0.354	0.746	0.002
Treatment response							
P + SD	0.55 ± 3.97	1.41 ± 3.12	0.61 ± 3.43	1.10 ± 4.53	1.12 ± 3.55	2.06 ± 3.57	0.92 ± 4.34
CR + PR	3.75 ± 3.32	3.21 ± 3.23	3.20 ± 3.48	3.32 ± 3.51	2.47 ± 3.56	2.48 ± 3.32	2.86 ± 3.48
p-value	<0.001	0.004	<0.001	0.003	0.018	0.356	0.006
Age							
≤ 75	2.06 ± 3.91	2.12 ± 3.25	1.86 ± 3.58	2.21 ± 3.98	1.49 ± 3.40	2.26 ± 3.37	2.04 ± 4.11
> 75	4.34 ± 3.32	4.08 ± 3.03	3.58 ± 3.77	3.50 ± 4.32	3.77 ± 3.85	2.54 ± 3.64	2.42 ± 3.19
p-value	0.008	0.008	0.092	0.216	0.008	0.691	0.955
Tumor location							
Breast	2.26 ± 3.90	2.11 ± 2.51	2.26 ± 3.45	2.63 ± 3.25	1.84 ± 3.25	1.74 ± 2.70	2.74 ± 3.33
Lung	2.76 ± 3.85	2.74 ± 3.51	2.05 ± 3.72	2.33 ± 3.87	2.05 ± 3.81	2.17 ± 3.46	2.48 ± 3.79
Prostate	3.36 ± 3.39	2.41 ± 3.86	2.27 ± 3.21	2.05 ± 4.10	2.50 ± 3.91	2.32 ± 3.77	1.73 ± 3.69
Others	2.00 ± 4.19	2.56 ± 3.17	2.31 ± 3.94	2.73 ± 4.60	1.64 ± 3.47	2.71 ± 3.51	1.71 ± 4.43
p-value	0.766	0.949	0.823	0.696	0.924	0.736	0.609
ECOG							
0–1	2.31 ± 3.87	2.40 ± 3.25	2.00 ± 3.58	2.24 ± 3.97	1.63 ± 3.37	2.51 ± 3.34	2.04 ± 3.78
≥ 2	2.93 ± 3.94	2.75 ± 3.41	2.61 ± 3.84	2.91 ± 4.25	2.57 ± 3.97	1.95 ± 3.55	2.27 ± 4.26
p-value	0.553	0.483	0.397	0.464	0.127	0.419	0.591
Pain score							
≤ 7	1.71 ± 4.01	2.30 ± 3.19	1.89 ± 3.53	2.46 ± 4.12	1.38 ± 3.07	1.88 ± 3.17	1.76 ± 4.36
≥ 8	3.15 ± 3.64	2.69 ± 3.38	2.46 ± 3.78	2.47 ± 4.05	2.40 ± 3.93	2.67 ± 3.57	2.39 ± 3.57
p-value	0.049	0.440	0.415	0.855	0.081	0.142	0.611
Radiation schedule							
Multiple	2.77 ± 3.91	2.61 ± 3.31	2.41 ± 3.53	2.78 ± 3.76	2.14 ± 3.74	2.25 ± 3.32	2.11 ± 4.01
Simple	2.11 ± 3.94	2.46 ± 3.25	2.05 ± 3.96	1.95 ± 4.56	1.78 ± 3.08	2.46 ± 3.54	2.21 ± 3.53
p-value	0.327	0.564	0.508	0.220	0.680	0.776	0.875
Chemotherapy							
No	2.61 ± 3.94	2.67 ± 3.40	2.43 ± 3.45	2.36 ± 4.05	2.01 ± 3.50	2.61 ± 3.37	2.19 ± 4.12
Yes	2.41 ± 3.86	2.34 ± 3.17	1.93 ± 3.94	2.61 ± 4.12	1.80 ± 3.75	1.95 ± 3.46	2.02 ± 3.70
p-value	0.797	0.612	0.448	0.446	0.822	0.227	0.717
Bisphosphonates							
No	2.29 ± 3.84	2.52 ± 3.26	2.20 ± 3.55	2.35 ± 3.79	2.17 ± 3.48	2.71 ± 3.28	1.99 ± 4.02
Yes	3.14 ± 4.03	2.51 ± 3.42	2.23 ± 4.02	2.77 ± 4.76	1.37 ± 3.89	1.29 ± 3.59	2.45 ± 3.72
p-value	0.235	0.778	0.834	0.359	0.283	0.021	0.599

*Normal work: includes both work outside the home and housework; P — progression; SD — stable disease; CR — complete response; PR — partial response; ECOG — Eastern Cooperative Oncology Group

results, radiation is an effective local therapy for patients with symptomatic bone metastases to improve patient's QoL. The results of this study are in line with other international studies [2, 5–10, 18]. In the present study, OR rate (including partial and complete responses) 4-weeks after treatment was 61.7%, comparable to those cited in the literature [19]. Indeed, presenting a favourable pain re-

Table 4. Multivariate analysis

Variable	p-value	Beta	95% confidence interval	
			Inferior	Superior
General activity				
Responders to RT (CR + PR)	< 0.001	2.9	1.6	4.2
> 75 years	0.048	1.6	0.01	3.2
Mood				
Responders to RT (CR + PR)	0.009	1.5	0.40	2.7
> 75 years	0.026	1.6	0.19	3.0
Walking ability				
Responders to RT (CR + PR)	< 0.001	2.6	1.3	3.8
Normal Work				
Responders to RT (CR + PR)	0.002	2.2	0.80	3.6
Relations with other people				
> 75 years	0.004	2.3	0.76	3.8
Sleep				
Bisphosphonates (yes)	0.035	–1.4	–2.7	–0.10
Enjoyment of life				
Responders to RT (CR + PR)	0.011	1.8	0.41	3.1
Gender (woman)	0.009	1.8	0.46	3.2

RT — radiation therapy; CR — complete response; PR — partial response; SD — stable disease; P — progression

sponse also associated with a statistically significant QoL improvement in all the functional interference items, except sleeping.

Previous studies have also reported that patients with painful bone metastases responding to RT show a better QoL than non-responders. However, they could not predict which patients would respond to RT. Therefore, RT should be offered to all patients with symptomatic bone metastases [7]. According to our results, pre-treatment clinical variables are not useful to predict the impact of RT on post-treatment QoL (Tab. 2). For example, several publications showed that treatment decisions might be different between elderly and younger patients. Moreover, elderly patients are less likely to receive palliative RT [20, 21]. However, the present study shows that older patients can benefit equally, or even more (regarding general activity, mood, and relationships with other people) than their younger counterparts (Tab. 2). In addition, patients with higher pre-treatment pain score (≥ 8) also benefited as much as patients with lower pain scores regarding QoL improvement. Therefore, QoL improvement after RT should be expected even in fragile older patients with lower ECOG performance status, independently of the primary tumor location, or the type of radiation schedule administered (Tab. 2).

Westhoff et al. [12] presented QoL outcomes from the Dutch Bone Metastases Study. The evaluation of physical symptomatology and functional status showed that although RT provided a meaningful pain response, the level of QoL remained stable. Moreover, according to Westhoff et al., in general, treatment with RT was not associated with an improvement of most QoL domains. Indeed, only psychosocial domain improved after treatment.

Caissie et al. [22] stated that RT responders show not only an improvement in pain, but also in QoL according to the QLQ-C15-PAL questionnaire. Moreover, one month after RT, responders showed an improvement in emotional functioning, including a decrease in symptoms such as insomnia and constipation.

Several questionnaires have been used to assess the ability of the RT to improve the QoL. Therefore, some studies are not directly comparable with the present study because different QoL questionnaires have been used. Nevertheless, the BPI as well as QLQ-BM 22 can differentiate between patients with varying responses and are indicated

for use in future clinical trials including patients with bone metastasis. We used the self-administered BPI questionnaire during the patients' visits. This simple evaluation instrument addresses the description and location of pain; and the level of relief that the treatment provides [15, 23]. In summary, we showed that the BPI is helpful to differentiate patients who respond to treatment from those who do not, observing an improvement in the 7 functional BPI items at the end of RT (Fig. 1). Wu et al. [5] also reported similar results in the BPI global improvement but, unlike in our study, these authors did not differentiate between responders to RT and non-responders.

As early as four weeks after RT, a pain response was reported by our patients. This fact was associated with a statistically significant improvement in QoL in all the elements of functional interference, except sleeping quality (Tab. 2 and Fig. 2). Zeng et al. [24] reported similar results one month after RT. Additionally, they observed non-significant sleep variations in the second and fourth months after treatment. Unlike these results, Khan et al. [25] showed an improvement in sleeping at the second and third month after RT in patients responding to RT.

Patients presenting with an initial pain score ≥ 8 showed a significant higher improvement in the general activity ($p = 0.049$), compared to patients with a baseline pain score < 8, although no other differences were found according to any other functional interference items (Tab. 2). Wu et al. [5] using the BPI questionnaire, reported similar results. They showed that the overall improvement in pain was correlated with a decrease in functional interference in patients receiving RT with palliative intent for painful bone metastases. Hence, the relationship between pain and general activity reinforces the relevance of pain reduction as a goal of palliative RT.

Interestingly, in our study responders had significantly greater improvement in functional psychosocial aspects (such as relations with others, and life enjoyment) compared with nonresponders. McDonald et al. [9] and Whestoff et al. [12] have also reported similar results. Conversely, other authors [8, 10] have reported opposite results. The difficulty in achieving statistical significance in these studies is likely explained by their limited sample size. Additionally, we should consider that psychosocial aspects may not be completely influenced by pain alone, but also by several symptoms such as fatigue, nausea, or appetite loss [26].

We acknowledge EORTC QLQ-BM22 was specifically designed and validated to evaluate QoL in patients with bone metastasis providing a more comprehensive evaluation of QoL than BPI. Brief pain inventory, however, is designed to evaluate functional interference in different clinical settings, including also patients with bone metastasis undergoing palliative radiotherapy (2–4). When evaluating interventions for cancer pain, improving pain interference in daily activities, rather than mere pain reduction, is a desirable endpoint for palliative radiation therapy. In this context, BPI is considered a validated tool in this clinical scenario (2–4). Therefore, we decided to use the BPI short form to evaluate the intensity of pain and the pain interference in patient's life.

In our study, patients > 75 years old presented a significantly higher improvement in general activity, mood and relationships with others compared with younger patients ($p = 0.008$) (Tab. 2 and Fig. 3). Hence, an older age should not be a reason to withhold palliative RT [17].

There might be other variables that can influence the improvement in QoL in addition to the effect of RT, and they could impact the outcomes observed in functional interference items included in BPI. However, we found that ECOG, chemotherapy, primary tumor location and RT schedule were not significantly related with any of the functional interference items. Therefore, RT treatment should not be declined based on clinical variables as, in general, they do not predict different results regarding QoL after palliative RT.

When we compared the QoL scores between the 2 most used schemes of RT (multiple fractions, 20 Gy/4–5 fractions *vs.* 8 Gy/L fraction), we found no significant differences in any QoL domains. Other authors founded similar results [18]. Therefore, a single fraction should be offered to these patients, especially to those presenting with short life expectancy.

We must highlight the limitations of the present study which include the relatively small sample size recruited and the reduction of the sample size for final analysis to 128 patients. However, loss to follow-up is a common issue regarding patients with metastatic disease. We have only

collected the first month's BPI. This interval was chosen because most patients usually have already responded and was not extended further to avoid interference with other additional therapies that patients may receive in the future. This limited BPI follow-up one month after RT prevents assessment of long-term outcomes regarding QoL. However, according to our results, patients undergoing palliative RT experience pain response and subsequent quality of live improvement already at four weeks after treatment. Although median time to response after radiotherapy is around 4 weeks, we acknowledge that some patients may experience pain response before or even 4 weeks after radiotherapy. Therefore, this study did not evaluate possible further responses to radiotherapy including QoL on earlier and later points in time as previously described by other authors

Moreover, McDonald et al. [9] showed that forty percent of patients experienced pain reduction and QoL improvement in earlier time points (such as 10 days after RT) with further improvements for most QoL domains at day 42 in patients responding to RT. Therefore, these results enhance the fact that RT should be offered even for those patients that present a limited expected survival.

Finally, in our series, as in most of the published series, the treatment of bone metastases is performed with conformal 3D-RT; however, some authors have studied the possibility of applying more modern techniques such as SBRT. Nguyen et al. [27] found in a phase II trial that SBRT had higher rates of pain response. Indeed, several studies have been published comparing the effectiveness between SBRT and conventional RT [32–37]. Indeed, there are potential disadvantages of SBRT, including possible increased pain flare or a higher incidence of radiation-induced fractures [38]. However, if a dose-escalated approach within the context SBRT could improve the pain response to radiotherapy and reduce acute toxicity, this would have a significant impact on the QoL for a large number of patients with advanced metastatic disease. In this context, there is a future avenue of research to confirm this hypothesis [38].

Conclusions

There is a significant correlation between pain reduction and improvement in functional interference items (including physical and psychosocial aspects) in patients with bone metastasis undergoing palliative RT, regardless of treatment fractionation and pretreatment clinical variables (such as age, gender, ECOG, tumor location or pretreatment pain intensity score).

Conflict of interests

The authors declare that they have no competing interests.

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Authors' contribution

V.C., A.G.I., D.R., O.O and J.C. collected, analyzed and interpreted the patient data and wrote the whole manuscript; R.C. and J.L.L.G were major contributors in writing the manuscript; A.N., V.M., A.I.V and F.C performed all radiation therapy dosimetry plans; J.C., L.M.I., P.W., A.G.I and D.R contributed to radiation treatment of all patients and reviewed the manuscript. All authors read and approved final manuscript.

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References

1. Pituskin E, Fairchild A, Dutka J, et al. Multidisciplinary team contributions within a dedicated outpatient palliative radiotherapy clinic: a prospective descriptive study. Int J Radiat Oncol Biol Phys. 2010; 78(2): 527–532, doi: 10.1016/j.ijrobp.2009.07.1698, indexed in Pubmed: 20100640.
2. Lutz S, Berk L, Chang E, et al. American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011; 79(4): 965–976, doi: 10.1016/j.ijrobp.2010.11.026, indexed in Pubmed: 21277118.
3. Sze WM, Shelley MD, Held I, et al. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy--a systematic review of randomised trials. Clin Oncol (R Coll Radiol). 2003; 15(6): 345–352, doi: 10.1016/s0936-6555(03)00113-4, indexed in Pubmed: 14524489.
4. Lee J, Hodgson D, Chow E, et al. A phase II trial of palliative radiotherapy for metastatic renal cell carcinoma. Cancer. 2005; 104(9): 1894–1900, doi: 10.1002/cncr.21410, indexed in Pubmed: 16177996.
5. Wu JSY, Monk G, Clark T, et al. Palliative radiotherapy improves pain and reduces functional interference in patients with painful bone metastases: a quality assurance study. Clin Oncol (R Coll Radiol). 2006; 18(7):

539–544, doi: 10.1016/j.clon.2006.05.003, indexed in Pubmed: 16969984.
6. Westhoff PG, de Graeff A, Reyners AKL, et al. Dutch Bone Metastasis Study Group. Effect of age on response to palliative radiotherapy and quality of life in patients with painful bone metastases. Radiother Oncol. 2014; 111(2): 264–269, doi: 10.1016/j.radonc.2014.03.017, indexed in Pubmed: 24746581.
7. Westhoff PG, de Graeff A, Monninkhof EM, et al. Dutch Bone Metastasis Study Group. Quality of Life in Relation to Pain Response to Radiation Therapy for Painful Bone Metastases. Int J Radiat Oncol Biol Phys. 2015; 93(3): 694–701, doi: 10.1016/j.ijrobp.2015.06.024, indexed in Pubmed: 26281825.
8. Zeng L, Chow E, Bedard G, et al. Quality of life after palliative radiation therapy for patients with painful bone metastases: results of an international study validating the EORTC QLQ-BM22. Int J Radiat Oncol Biol Phys. 2012; 84(3): e337–e342, doi: 10.1016/j.ijrobp.2012.05.028, indexed in Pubmed: 22763028.
9. McDonald R, Ding K, Brundage M, et al. Effect of Radiotherapy on Painful Bone Metastases: A Secondary Analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23. JAMA Oncol. 2017; 3(7): 953–959, doi: 10.1001/jamaoncol.2016.6770, indexed in Pubmed: 28196208.
10. Mendez LC, Raman S, Wan BoA, et al. Quality of life in responders after palliative radiation therapy for painful bone metastases using EORTC QLQ-C30 and EORTC QLQ-BM22: results of a Brazilian cohort. Ann Palliat Med. 2017; 6(Suppl 1): S65–S70, doi: 10.21037/apm.2017.04.06, indexed in Pubmed: 28595442.
11. Weinfurt KP, Li Y, Castel LD, et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005; 16(4): 579–584, doi: 10.1093/annonc/mdi122, indexed in Pubmed: 15734776.
12. Westhoff PG, Verdam MGE, Oort FJ, et al. Dutch Bone Metastasis Study Group. Course of Quality of Life After Radiation Therapy for Painful Bone Metastases: A Detailed Analysis From the Dutch Bone Metastasis Study. Int J Radiat Oncol Biol Phys. 2016; 95(5): 1391–1398, doi: 10.1016/j.ijrobp.2016.03.032, indexed in Pubmed: 27315664.
13. Gomez-Iturriaga A, Cacicedo J, Navarro A, et al. Incidence of pain flare following palliative radiotherapy for symptomatic bone metastases: multicenter prospective observational study. BMC Palliat Care. 2015; 14: 48, doi: 10.1186/s12904-015-0045-8, indexed in Pubmed: 26427616.
14. Cleeland C. Measurement of pain by subjective report. Adv Pain Res Ther Issues Pain Manag. 1989; 12.
15. Cleeland CS. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap. 1994; 23(2): 129–138.
16. Chow E, Hoskin P, Mitera G, et al. International Bone Metastases Consensus Working Party. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Int J Radiat Oncol Biol Phys. 2012; 82(5): 1730–1737, doi: 10.1016/j.ijrobp.2011.02.008, indexed in Pubmed: 21489705.
17. Cacicedo J, Gómez-Iturriaga A, Navarro A, et al. Analysis of predictors of pain response in patients with bone metastasis undergoing palliative radiotherapy: Does age matter? J Med Imaging Radiat Oncol. 2018 [Epub ahead of print], doi: 10.1111/1754-9485.12749, indexed in Pubmed: 29797486.
18. Arias F, Arrarás JI, Asín G, et al. To What Extent Does Radiotherapy Improve the Quality of Life of Patients With Bone Metastasis?: A Prospective, Single-Institutional Study. Am J Clin Oncol. 2018; 41(2): 163–166, doi: 10.1097/COC.0000000000000249, indexed in Pubmed: 26535991.
19. Culleton S, Kwok S, Chow E. Radiotherapy for pain. Clin Oncol (R Coll Radiol). 2011; 23(6): 399–406, doi: 10.1016/j.clon.2010.11.011, indexed in Pubmed: 21168999.
20. Lavergne MR, Johnston GM, Gao J, et al. Variation in the use of palliative radiotherapy at end of life: examining demographic, clinical, health service, and geographic factors in a population-based study. Palliat Med. 2011; 25(2): 101–110, doi: 10.1177/0269216310384900, indexed in Pubmed: 20937613.
21. Murphy JD, Nelson LM, Chang DT, et al. Patterns of care in palliative radiotherapy: a population-based study. J Oncol Pract. 2013; 9(5): e220–e227, doi: 10.1200/JOP.2012.000835, indexed in Pubmed: 23943892.
22. Caissie A, Zeng L, Nguyen J, et al. Assessment of health-related quality of life with the European Organization for Research and Treatment of Cancer QLQ-C15-PAL after palliative radiotherapy of bone metastases. Clin Oncol (R Coll Radiol). 2012; 24(2): 125–133, doi: 10.1016/j.clon.2011.08.008, indexed in Pubmed: 21917431.
23. Badia X, Muriel C, Gracia A, et al. Validación española del cuestionario Brief Pain Inventory en pacientes con dolor de causa neoplásica. Med Clínica. 2003; 120(2): 52–59, doi: 10.1016/s0025-7753(03)73601-x.
24. Zeng L, Chow E, Zhang L, et al. Comparison of pain response and functional interference outcomes between spinal and non-spinal bone metastases treated with palliative radiotherapy. Support Care Cancer. 2012; 20(3): 633–639, doi: 10.1007/s00520-011-1144-6, indexed in Pubmed: 21476118.
25. Khan L, Uy C, Nguyen J, et al. Self-reported rates of sleep disturbance in patients with symptomatic bone metastases attending an outpatient radiotherapy clinic. J Palliat Med. 2011; 14(6): 708–714, doi: 10.1089/jpm.2010.0491, indexed in Pubmed: 21554034.
26. Bernhard J, Ganz PA. Psychosocial issues in lung cancer patients (Part 1). Chest. 1991; 99(1): 216–223, doi: 10.1378/chest.99.1.216, indexed in Pubmed: 1984958.
27. Yamaguchi K, Saito T, Toya R, et al. Palliative radiotherapy for painful lymph node metastases. Radiat Oncol. 2021; 16(1): 178, doi: 10.1186/s13014-021-01900-8, indexed in Pubmed: 34530897.
28. Chow E, James J, Barsevick A, et al. Confirmatory factor analysis of brief pain inventory (BPI) functional interference clusters in patients with bone metastases. J Pain Manag. 2010; 3(3): 247–253, indexed in Pubmed: 21686033.
29. Saito T, Nakamura N, Murotani K, et al. Index and Nonindex Pain Endpoints in Radiation Therapy for Painful Tumors: A Secondary Analysis of a Prospective Observational Study. Adv Radiat Oncol. 2020; 5(6): 1118–1125, doi: 10.1016/j.adro.2020.09.013, indexed in Pubmed: 33305072.
30. Roos DE, Turner SL, O'Brien PC, et al. Trans-Tasman Radiation Oncology Group, TROG 96.05. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). Radiother Oncol. 2005; 75(1): 54–63, doi: 10.1016/j.radonc.2004.09.017, indexed in Pubmed: 15878101.

31. Cacicedo J, Ciria JP, Morillo V, et al. Pain response and quality of life assessment in patients with moderate/severe neuropathic pain due to bone metastasis undergoing treatment with palliative radiotherapy and tapentadol: A prospective multicentre pilot study. J Med Imaging Radiat Oncol. 2020; 64(6): 859–865, doi: 10.1111/1754-9485.13088, indexed in Pubmed: 32729219.
32. Nguyen QN, Chun SG, Chow E, et al. Single-Fraction Stereotactic vs Conventional Multifraction Radiotherapy for Pain Relief in Patients With Predominantly Nonspine Bone Metastases: A Randomized Phase 2 Trial. JAMA Oncol. 2019; 5(6): 872–878, doi: 10.1001/jamaoncol.2019.0192, indexed in Pubmed: 31021390.
33. Sprave T, Verma V, Förster R, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. Radiother Oncol. 2018; 128(2): 274–282, doi: 10.1016/j.radonc.2018.04.030, indexed in Pubmed: 29843899.
34. Gillespie EF, Lapen K, Wang DG, et al. Replacing 30 Gy in 10 fractions with stereotactic body radiation therapy for bone metastases: A large multi-site single institution experience 2016-2018. Clin Transl Radiat Oncol. 2020; 25: 75–80, doi: 10.1016/j.ctro.2020.10.001, indexed in Pubmed: 33102818.
35. Cellini F, Manfrida S, Deodato F, et al. Pain REduction with bone metastases STereotactic radiotherapy (PREST): A phase III randomized multicentric trial. Trials. 2019; 20(1): 609, doi: 10.1186/s13063-019-3676-x, indexed in Pubmed: 31661034.
36. Spencer KL, van der Velden JM, Wong E, et al. Systematic Review of the Role of Stereotactic Radiotherapy for Bone Metastases. J Natl Cancer Inst. 2019; 111(10): 1023–1032, doi: 10.1093/jnci/djz101, indexed in Pubmed: 31119273.
37. Pielkenrood BJ, Gal R, Kasperts N, et al. Quality of Life After Stereotactic Body Radiation Therapy Versus Conventional Radiation Therapy in Patients With Bone Metastases. Int J Radiat Oncol Biol Phys. 2022; 112(5): 1203–1215, doi: 10.1016/j.ijrobp.2021.12.163, indexed in Pubmed: 35017007.
38. Mercier C, Dirix P, Ost P, et al. A phase III randomized-controlled, single-blind trial to improve quality of life with stereotactic body radiotherapy for patients with painful bone metastases (ROBOMET). BMC Cancer. 2019; 19(1): 876, doi: 10.1186/s12885-019-6097-z, indexed in Pubmed: 31484505.