Original Article

Clinical Predictors for Analgesic Response to Radiotherapy in Patients with Painful Bone Metastases

Ragnhild Habberstad, MD, Trude Camilla S. Frøseth, MSc, Nina Aass, MD, PhD, Ellen Bjerkeset, MSc, Tatiana Abramova, MD, Elena Garcia-Alonso, MD, Mariangela Caputo, MD, Romina Rossi, MD, PhD, Jason W. Boland, MD, PhD, Cinzia Brunelli, PhD, Jo-Åsmund Lund, MD, PhD, Stein Kaasa, MD, PhD, and Pål Klepstad, MD, PhD

European Palliative Care Research Centre (PRC), Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU (R.H., T.C.S.F., P.K.), Norwegian University of Science and Technology and St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway; Cancer Clinic, St. Olavs hospital, Trondheim University Hospital (R.H., T.C.S.F.), Trondheim, Norway; European Palliative Care Research Centre (PRC), Department of Oncology (N.A., S.K.), Oslo University Hospital, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway; Regional Advisory Unit for Palliative Care, Department of Oncology (E.B.), Oslo University Hospital, Oslo, Norway; Dept. Oncology, Ålesund Hospital (T.A.), Møre and Romsdal Hospital Trust, Ålesund, Norway; Radiation Oncology Department Arnau de Vilanova University Hospital. IRB Lleida (E.G.-A.), España; Radiation Oncology 1, Palliative Care Pain Therapy and Rehabilitation (M.C.), Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Palliative Care and Pain Therapy Unit (R.R.), Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS; Wolfson Palliative Care Research Centre (J.W.B.), Hull York Medical School, University of Hull, Hull, UK; Palliative Care, Pain Therapy and Rehabilitation Unit (C.B.), Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences (J.-\.-Å.L.), Norwegian University of Science and Technology, Trondheim, Norway; Department of Oncology (J.-\.-Å.L.), Ålesund Hospital, Møre og Romsdal Hospital Trust, Ålesund, Norway; Department of Health Sciences, Faculty of Medicine and Health Sciences (J.-\.-Å.L.), NTNU Ålesund; Department of Circulation and Medical Imaging (P.K.), Norwegian University of Science and Technology (NTNU), Trondheim, Norway; Department of Anesthesiology and Intensive Care Medicine (P.K.), St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

Abstract

Background. Radiotherapy (RT) reduces pain in about 60% of patients with painful bone metastases, leaving many patients without clinical benefit. This study assesses predictors for RT effectiveness in patients with painful bone metastases.

Materials and methods. We included adult patients receiving RT for painful bone metastases in a multicenter, multinational longitudinal observational study. Pain response within 8 weeks was defined as ≥2-point decrease on a 0−10 pain score scale, without increase in analgesics; or a decrease in analgesics of ≥25% without increase in pain score. Potential predictors were related to patient demographics, RT administration, pain characteristics, tumor characteristics, depression and inflammation (C-reactive protein [CRP]). Multivariate logistic regression analysis with multiple imputation of missing data were applied to identify predictors of RT response.

Results. Of 513 eligible patients, 460 patients (90 %) were included in the regression model. 224 patients (44%, 95% confidence interval (CI) 39%−48%) responded to RT. Better Karnofsky performance status (Odds ratio (OR) 1.39, CI 1.15−1.68), breast cancer (OR 2.54, CI 1.12−5.73), prostate cancer (OR 2.83, CI 1.27−6.33) and soft tissue expansion (OR 2.00, CI 1.23−3.25) predicted RT response. Corticosteroids were a negative predictor (OR 0.57, CI 0.37−0.88). Single and multiple fraction RT had similar response. The discriminative ability of the model was moderate; C-statistic 0.69.

Conclusion. This study supports previous findings that better performance status and type of cancer diagnosis predicts analgesic RT response, and new data showing that soft tissue expansion predicts RT response and that corticosteroids is a negative

Abbreviations: RT, Radiotherapy; CRP, C-reactive protein; CT, Computerized tomography; LANSS, The Leeds Assessment of Neuropathic Symptoms and Signs; PHQ9, The Patient Health Questionnaire Depression Scale; MI, Multiple imputation; MICE, Multivariate imputation by chained equations; MAR, missing at random; CC, Complete case analysis; C-statistics, Concordance statistics

Address correspondence to: Ragnhild Habberstad, MD, European Palliative Care Research Centre (PRC), Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU). P.O.Box 8905. 7491 Trondheim, Norway, E-mail: ragnhild.habberstad@gmail.com

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predictor for RT response in patients with painful bone metastases. J Pain Symptom Manage 2021;62:681−690.

Key Words
Cancer, radiotherapy, palliative, bone metastases, pain, inflammation

Key Message

This is the first prospective multicenter study to investigate predictors of RT response in patients with painful bone metastases. Performance status, cancer diagnosis and soft tissue expansions predicted RT response, while use of corticosteroids was a negative predictor. These results may be helpful in selecting patients for palliative RT.

Introduction

Pain is a frequent and feared consequence of cancer. Bone metastases are the cause of pain in in up to 45 % of patients with cancer pain.[1,2] Treatment of painful bone metastases include analgesic medications combined with anti-cancer treatment including radiotherapy (RT). RT is well-established for painful bone metastases with about 60% of patients that respond to treatment. In the non-responders other pain reliving interventions may be delayed waiting for a potential RT response that can occur weeks after treatment.[3] Many patients with bone metastases have a short life expectancy, and it is important to avoid ineffective treatments that are time-consuming and have a risk of adverse effects.

In previous trials investigating clinical predictors of RT response in patients with painful bone metastases, breast or prostate cancer and better performance status have been associated with RT response.[4,5] Higher baseline pain intensity, absence of visceral metastasis, the use of opioids and younger age may increase the likelihood of RT response, but the published results are inconsistent.[4−7] Neuropathic pain, physical activity and spinal metastases have not predicted RT response.[8−11] Depression is associated with pain in cancer patients, but as far as we know it is not previously investigated in respect to RT response.[12]

Different imaging techniques are investigated in respect to RT response in patients with painful bone metastases, but the findings are so far inconclusive.[11] Radiological scans may reveal soft tissue expansions outside bone or classify metastases as osteolytic or osteoblastic (sclerotic). A small trial on spinal bone metastases concluded with no significant difference in analgesic response rates if soft tissue expansions were present.[13] As far as we know analgesic RT response in osteolytic metastases compared to osteoblastic (sclerotic) metastases are not previously investigated based on radiological appearance, but two trials have reported increased levels of urinary osteoclast markers in patients with no RT response.[14,15]

The mechanisms of pain relief after RT is partly due to shrinkage of the tumor volume. The immediate effect of RT is also proposed to be related to inhibition of inflammatory mediators.[16] Pre-clinical studies have demonstrated the importance of inflammatory mediators in cancer induced bone pain,[17] and in one study the systemic inflammatory biomarker C-reactive protein (CRP) was associated with cancer pain intensity.[18]Only two previously published papers have investigated multiple factors of RT response,[4,5] both resulted in a predictive model with low to moderate discriminative ability. One reason for this may be that relevant predictors were not included in the models. The present study was designed to in addition to established predictors add the potential predictors radiological appearance of metastases, pain characteristics, depression and inflammation to the model in order to observe if this improves the ability to appropriately select patients for RT.[11] Thus. the aim of this prospective, multicenter study was to investigate which factors are associated with RT response in patients with painful bone metastases.

Material and Methods

Study Population

Adult patients (≥18 years) with a verified cancer diagnosis about to undergo RT with a palliative intent for painful bone metastases were included in this longitudinal observational multicenter study. RT was initiated within one week after baseline observations. Patients who received RT within the preceding 4 weeks before the study and patients with long bone pathological fractures were not included. Patients with several RT treatments were included in the study once. Patients with RT indications other than pain, such as spinal cord compression with a risk for paralysis, were not included. Enrolled patients with a worst pain score less than two at baseline were not included in analyses.[19] Patients were recruited from seven oncological centers across Europe (Norway, Italy, Spain and UK) from December 2013 to December 2017.[20] Collaborating centers in the European Palliative Care Research Centre were invited to contribute in the PRAIS study. Study information were also distributed at

international meetings and congresses prior to initiation of the study. Before the start of inclusion, the study was registered at ClinicalTrials.gov (NCT02107664).

Study Procedure and Outcome Measures

The following information were collected: age, gender, cancer diagnosis, osteolytic metastases and soft tissue expansion at each radiation site assessed by Computerized Tomography (CT) before RT (yes/no/not evaluable), RT fraction and total dose, location in weight bearing bone (yes/no), opioid dose (oral morphine equivalents last 24hours)[21] and the use of corticosteroids (yes/no). Comorbidity and performance status were assessed by Charlson Comorbidity Index (range 0-37)[22] and Karnofsky performance status (range 0−100),[23] respectively. Patient reported outcomes were: pain at rest and at movement from each irradiated site (11-point numeric rating scale); with the worst baseline pain score used in calculate RT response, episodic pain (yes/no), neuropathic symptoms assessed by The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (range 0−5) [24] and depressive symptoms assessed by The Patient Health Questionnaire Depression Scale (PHQ9) (range 0−29).[25] Blood samples were taken before RT, and CRP was analyzed at the local laboratory in each study center. Baseline observations used in the predictive analyses of RT response were obtained within one week before the start of RT. To calculate RT response self-reported pain scores and opioid doses were obtained at 3 and 8 weeks after the last RT fraction (+/- 3 days). We aimed to consecutively include all patients admitted to RT for painful bone metastases, although this was not possible due to organizational issues in three of the including sites. If patients were unable to attend the hospital for follow-up, one of the investigators contacted the patients by phone and patients received the questionnaires by postal mail. A written guidance for data recording was distributed to all collaborating centers, and the centers could at all times contact the principal investigator. All results were manually controlled by two of the investigators (RH, TCSF) and if inconsistencies the recorded result were checked by the local investigator.

Response Definition

The primary outcome was "response to RT for painful bone metastases". Response within 8 weeks after the last RT fraction was defined as at least a 2-point decrease in the worst pain score at the irradiated site without increase in analgesic use or reduction in opioid dose of at least 25% from baseline without an increase in pain score at the irradiated site.[26] Patients with two or more radiation locations were defined as responders if they responded in at least one of the irradiated sites.

Statistical Analyses

Sample size calculation was based upon analgesic RT response as the primary dependent variable. A full statistical estimate of sample size requires knowledge of the variance-covariance matrix, which was not available at the planning stage of this study. Therefore, the widely used rule of thumb of 10 x number of variables was adopted and resulted in a need of 290 patients to be included in the study. To account for patients lost to follow up and possible unknown interactions, the number of patients was set to 600. The original protocol plan was to include a validation sample of additional 400 patients, but because of slow recruitment the analyses were performed without the planned validation sample.[20] Continuous variables are presented as means with standard deviation (SD) and categorical variables as frequencies with percentages. Potential predictors for RT response were chosen based upon previously described associations,[11] and putative clinical relationship. The 17 independent variables included in analyses are detailed in Table 3. Multivariate logistic regression analysis with multiple imputation (MI) of missing data using multivariate imputation by chained equations (MICE) were applied to identify predictors of RT response.[27] All potentially relevant variables were included in the multivariate model, without performing any variable selection in order not to lose any relevant correlation in the selection process and to obtain confidence intervals with proper coverage.[28] Missing variables were considered missing at random (MAR) and MI was chosen as it allows a considerable gain in estimates efficiency and is less biased than complete case analysis (CC) across a number of scenarios.[29] Missing variables were imputed 25 times. Patients missing the outcome variable (unknown RT response) were excluded from the analysis after imputation.[27] For the PHQ9 and LANSS score, missing items were replaced with the average value if less than half of the items were missing.[30] Imputation diagnostics were performed for all analyses. Since MI is not always better than CC for missing covariate problems,[29] sensitivity analyses (CC analysis, worst case analysis and best case analysis) were also performed to evaluate the strength of the imputed model (Supplementary 1). All regression models were adjusted by study centre in order to account for a potential centre effect [31]. Concordance statistics (C-statistics) were used to determine the goodness of fit.[32] Predictive probabilities were estimated from the complete case model for descriptive purposes. All analyses are performed using STATA v16 (Stata Corporation LP; College Station, TX, USA).

Ethics

A signed informed consent was obtained from all patients. The study was approved by The Regional Committee for Medical and Health Research Ethics

(2013/1126/REK midt) and by the regulatory authorities at each trial site.

Results

A total number of 574 patients were enrolled in the study. Sixty-one patients were not included in the analyses (Fig. 1). Complete data were available in 382 patients (74%), while 100 patients (19 %) had one missing variable and 31 patients (6%) had 2 or more missing variables.

Sixty-one percent were men and the most common cancer diagnoses were prostate (26%), breast (20%), lung (18%) and gastrointestinal (16%) cancer. The mean age was 66.1 years (SD 10.6). Multiple fractions and single fraction RT were given to 63% and 37% of patients, respectively (Table 1). The most common RT locations were spine (45%), pelvis (34%) and thorax (9%). Twenty-seven patients died within the first 3 weeks after RT and were not included in the final analysis and 67 patients died between 3 and 8 weeks after RT.

Of included patients 224 (44%, CI 39%-48%) responded to RT and 236 (46%, CI 42%-50%) did not respond to RT. Fifty-three (10%, CI 8%−13%) had an unknown RT response (Fig. 1). Among the 67 patients dying between 3 and 8 weeks after RT only 8 patients (12%) responded to RT. Baseline variables by response status are described in Table 2. Multiple imputation allowed the final regression models to be carried out on 460 patients (90% of the sample) after excluding the 53 patients with unknown RT response.

Better performance status (OR 1.39, CI 1.15−1.68), primary diagnosis of breast cancer (OR 2.54, CI 1.12−5.73) or prostate cancer (OR 2.83, CI 1.27−6.33) and soft tissue expansion outside bone (OR 2.00, CI 1.23−3.25) predicted RT response (*P*-value <0.05). The use of corticosteroids was a negative predictor for RT response (OR 0.57, CI 0.37-0.88). The discriminative ability of the model was moderate, with a C-statistic of 0.69 (Table 3, Fig. 2).

In patients with normal CRP 48 % responded to RT compared to 42% in patients with elevated CRP (Table 2), but CRP was not statistically significant in the multivariate model. There was no difference in response rates among patients receiving single compared to multiple RT fractions (Table 3). Sensitivity analyses with complete case analysis and patients with unknown RT response as worst case and best case displayed similar findings (Supplementary table 1).

Discussion

Our study shows that better performance status, primary cancer diagnosis of breast or prostate and presence of soft tissue expansion outside bone can positively predict effect of RT on bone pain in patients with painful bone metastases. The use of corticosteroids was a negative predictor for RT response.

In a systematic review, Gardner et al. identified eight studies evaluating clinical predictors for RT response.[4,5,7,9-11,33-35] Only two studies, both secondary analyses, included several potential predictors in a multivariate analysis.[4,5] Proposed factors in these two studies that could influence response to RT were breast and prostate as the primary cancer, high pain intensity, absence of visceral metastases, younger age, the use of opioids and better performance status. Both studies reported a low to moderate discriminative ability.[4,5] Based upon the findings, Gardner et al.[11] concluded

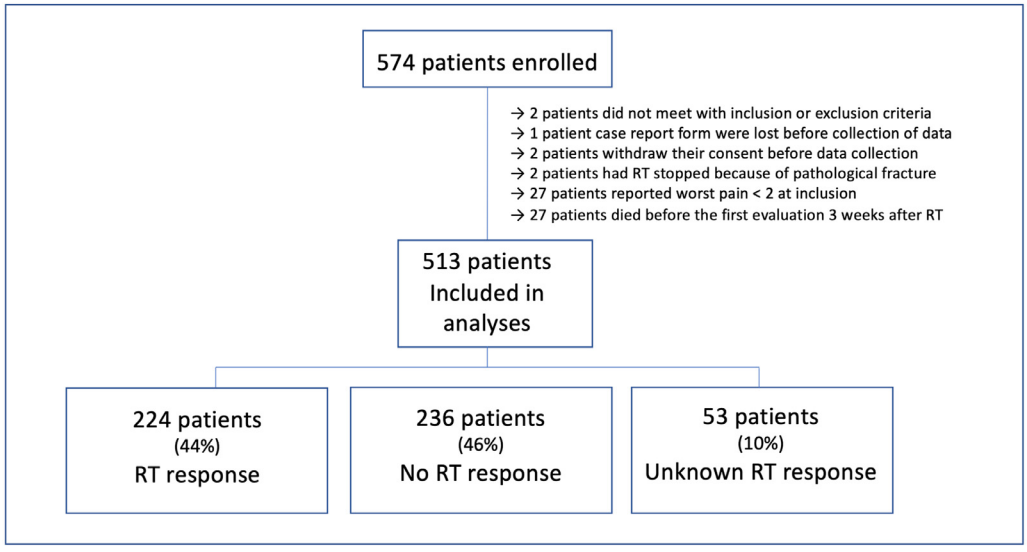

Fig. 1. Flowchart of included patients. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article

Table 1
Patient Characteristics at Baseline (N 513)

Baseline Variables	Number (%)	Mean (SD)
Age		66.1 (10.6)
Gender		
Male	314 (61%)	
Female	199 (39%)	
Charlson comorbidity index		6.5 (0.92)
Karnofsky performance status		72.6 (12.1)
Cancer diagnosis		
Gastrointestinal	81 (16%)	
Breast	103 (20%)	
Prostate	133 (26%)	
Lung	92 (18%)	
Urological	56 (11%)	
Other/unknown	48 (9%)	
Metastases		
Other sites than bone	319 (62%)	
Only bone	194 (38%)	
RT fraction		
Multiple fraction	325 (63%)	
Single fraction <=8 Gy	188 (37%)	
Soft tissue expansion at radiated site		
No	337 (66%)	
Yes	165 (32%)	
Not evaluable	11 (2%)	
Osteolytic metastases at radiated site		
No	289 (56 %)	
Yes	189 (37 %)	
Not evaluable	35 (7 %)	
Radiation location in weight bearing bone		
No	78 (15 %)	
Yes	435 (85 %)	
Maximum pain at radiated site last 24h		5.9 (2.2)
Episodic pain		
No	178 (35 %)	
Yes	313 (61%)	
Neuropathic pain symptoms (a)		1.1 (1.2)
Opioid dose (b)		75.0 (143.7)
Corticosteroids		
No	278 (54%)	
Yes	232 (45%)	
Depressive symptoms (c)		8.0 (4.8)
CRP		
Normal (<=5)	188 (37%)	
Elevated (>5)	281 (55%)	
Study center		
Lleida	19 (4 %)	
Milan	41 (8 %)	
Forli	26 (5%)	
Trondheim	212 (41%)	
Oslo	157 (31%)	
Aalesund	44 (9%)	
Hull	14 (3%)	

(a) Number of self-reported symptoms of neuropathic pain according to LANSS
(b) Opioid dose in oral morphine equivalents last 24h
(c) Number of depressive symptoms according to PHQ 9

that no clinical markers are applicable for clinical use. The lack of studies primarily designed to evaluate RT response for cancer bone pain warranted a prospective study primarily designed to identify multiple predictors for RT response.[4,5] Our study confirmed that better performance status and that a diagnosis of either breast or prostate cancer increased the chance of a benefit from palliative RT in patients with painful bone metastases.

In addition to previously proposed predictors for RT response we included information on tumor characteristics, inflammation, pain characteristics and depression. We observed that patients with soft tissue expansion outside the bone had 100% higher odds of responding to RT compared to patients without soft tissue expansion. A possible explanation for this finding is that patients with a soft tissue mass in relation to bone metastases might have more inflammation and edema causing pain and therefore are more responsive to RT. Our observation is opposite to Mitera et al.[13] who did not observe an association with soft tissue expansion and RT response. However, Mitera et al.[13] included only 33 patients all with spinal bone metastases which is a different sub-cohort compared to our sample.

Chow et al.[15] observed a higher level of urinary osteoclast markers in patients not responding to RT. Therefore, as osteolytic metastases have higher osteoclast activity, it could be expected that patients with osteolytic metastases had less RT response compared to sclerotic bone metastases. Despite this potential association, we did not observe a significant difference in RT response in respect to osteolytic versus sclerotic metastases.

It is suggested that the early pain relief from RT is due to an effect on inflammation.[16] A relationship between high level of inflammatory biomarkers and bone cancer pain intensity has been demonstrated.[17] CRP was chosen as a potential systemic inflammatory biomarker for RT response as it is associated with cancer pain and is routinely available.[18] In the multivariable model CRP did not predict RT response. CRP is a crude measure of inflammation and analyses on more specific inflammation biomarkers may reveal a relationship. Also, a RT effect on inflammation related to the bone metastases and surrounding tissue may not be reflected in a systemic inflammatory biomarker. Interestingly, patients using corticosteroids at baseline had a 57% lower odds of RT response compared to patients not using corticosteroids. Corticosteroids are known to reduce inflammation and are proposed to reduce the incidence of pain flares after RT.[36,37] One potential explanation for corticosteroids being a negative predictor for RT response is that the anti-inflammatory effect of RT is already induced by the corticosteroids which reduce the additional effect of RT. Corticosteroids are widely administered to patients with metastatic cancer disease and if has a negative impact on RT response, this could lead to a change in clinical practice. In this study a dose response relationship could not be investigated because corticosteroid doses were not available, nor was the analyses performed to evaluate the potential effect of corticosteroids as an adjunct during or after RT. Further research on the impact of corticosteroids on RT response is warranted.

Table 2
Baseline Variables by RT Response Status (N 513)

Baseline Variables	RT Response n (%)	No RT Response n (%)	Unknown RT Response n (%)
Age			
<50	22 (46 %)	20 (42 %)	6 (13 %)
51-70	125 (46 %)	127 (47 %)	21 (8 %)
>70	77 (40%)	89 (46 %)	26 (14 %)
Gender			
Male	138 (44 %)	143 (46 %)	33 (11 %)
Female	86 (43 %)	93 (47 %)	20 (10 %)
Charlson comorbidity index			
6 (only metastatic cancer disease)	145 (43%)	157 (47 %)	35 (10 %)
>6 (other comorbidities)	79 (45 %)	79 (45 %)	18 (10 %)
Karnofsky performance status			
<50	9 (25%)	18 (50%)	9 (25 %)
50−70	98 (38 %)	135 (52%)	25 (10 %)
80−100	117 (53%)	83 (38 %)	19 (9 %)
Cancer diagnosis			
Gastrointestinal	26 (32 %)	43 (53 %)	12 (15 %)
Breast	53 (51 %)	41 (40 %)	9 (9 %)
Prostate	67 (50 %)	53 (40 %)	13 (10 %)
Lung	36 (39 %)	50 (54 %)	6 (7 %)
Urological	23 (41 %)	29 (52 %)	4 (7 %)
Other/unknown	19 (40 %)	20 (42 %)	9 (19 %)
Metastases			
Other sites than bone	129 (40 %)	157 (49%)	33 (10 %)
Only bone	95 (49 %)	79 (41 %)	20 (10 %)
RT fraction			
Multiple fraction	140 (43 %)	147 (45 %)	38 (12 %)
Single fraction <=8 Gy	84 (45 %)	89 (47 %)	15 (8 %)
Soft tissue expansion at radiated site			
No	142 (42%)	162 (48 %)	33 (10 %)
Yes	79 (48 %)	67 (41 %)	19 (12 %)
Not evaluable	3 (27 %)	7 (64 %)	1 (9 %)
Osteolytic metastases at radiated site			
No	125 (43 %)	137 (47 %)	27 (9 %)
Yes	87 (46 %)	83 (44 %)	19 (10 %)
Not evaluable	12 (34 %)	16 (46 %)	7 (20 %)
Radiation location in weight bearing bone			
No	34 (44%)	37 (47 %)	7 (9 %)
Yes	190 (44 %)	199 (46%)	46 (11 %)
Maximum pain at radiated site last 24h			
2 – 4	56 (39%)	70 (49 %)	16 (11 %)
5 – 7	108 (47%)	102 (44 %)	21 (9 %)
8 t− 10	60 (43%)	64 (46%)	14 (10 %)
Episodic pain			
No	80 (45 %)	79 (44 %)	19 (11 %)
Yes	133 (42 %)	151 (48 %)	29 (9 %)
Neuropathic pain symptoms (a)			
No symptoms	93 (44 %)	98 (46 %)	21 (10 %)
One or more symptom	123 (44%)	130 (46 %)	27 (10 %)
Opioid dose (b)			
No opioids	57 (55 %)	41 (39 %)	6 (6 %)
< 60 mg	111 (46 %)	109 (45 %)	23 (9 %)
61−150 mg	33 (35 %)	51 (54 %)	11 (12 %)
>150 mg	23 (33 %)	34 (49%)	12 (17 %)
Corticosteroids			
No	138 (50 %)	117 (42 %)	23 (8 %)
Yes	86 (37 %)	117 (50 %)	29 (13 %)
Depressive symptoms (c)			
0−9	158 (48 %)	149 (45 %)	25 (8 %)
>=10	60 (38 %)	75 (48%)	22 (14 %)
CRP			
Normal (<=5)	91 (48 %)	77 (41 %)	20 (11 %)
Elevated (>5)	117 (42 %)	138 (49 %)	26 (9 %)

(a) Number of self-reported symptoms of neuropathic pain according to LANSS
(b) Opioid dose in oral morphine equivalents last 24h
(c) Number of depressive symptoms according to PHQ 9

Table 3
Multivariate Logistic Regression Model of Predictors of RT Response (N 460)

Independent variables	OR	95% CI
Age	0,99	[0.97,1.01]
Gender		
Male	1,00	[.,.]
Female	0,97	[0.54,1.75]
Charlson comorbidity index	1,12	[0.90,1.40]
Karnofsky performance status	**1,39*** **	**[1.15,1.68]**
Cancer diagnosis		
Gastrointestinal	1,00	[.,.]
Breast	**2,54***	**[1.12,5.73]**
Prostate	**2,83***	**[1.27,6.33]**
Lung	1,29	[0.61,2.71]
Urological	1,29	[0.58,2.89]
Other/unknown	1,60	[0.65,3.93]
Metastases		
Other sites than bone	1,00	[.,.]
Only bone	1,27	[0.80,2.02]
RT fraction		
Multiple fraction	1,00	[.,.]
Single fraction <=8 Gy	1,29	[0.80,2,09]
Soft tissue expansion at radiated site		
No	1,00	[.,.]
Yes	**2,00****	**[1.23,3.25]**
Not evaluable	0,68	[0.12,3.89]
Osteolytic metastases at radiated site		
No	1,00	[.,.]
Yes	1,18	[0.74,1.89]
Not evaluable	0,92	[0.34,2.47]
Radiation location in weight bearing bone		
No	1,00	[.,.]
Yes	1,24	[0.70,2.21]
Maximum pain at radiated site last 24h	1,07	[0.96,1.19]
Episodic pain		
No	1,00	[.,.]
Yes	0,91	[0.56,1.48]
Neuropathic pain symptoms (a)	0,99	[0.84,1.18]
Opioid dose (b)	1,00	[1.00,1.00]
Corticosteroids		
No	1,00	[.,.]
Yes	**0,57***	**[0.37,0.88]**
Depressive symptoms (c)	0,99	[0.94,1.04]
CRP		
Normal (<=5)	1,00	[.,.]
Elevated (>5)	0,91	[0.58,1.44]
C-statistics	**0,69**	

*** p<0.05, ** p<0.01, *** p<0.001**
(a) Number of self-reported symptoms of neuropathic pain according to LANSS
(b) Opioid dose in oral morphine equivalents last 24h
(c) Number of depressive symptoms according to PHQ 9

Several potential clinical variables did not significantly predict the response to palliative RT for bone cancer pain in the present study. This includes variables such as pain intensity,[4] age,[5] absence of visceral metastases,[5] tumor location[9,35] and neuropathic pain.[10] Furthermore, clinical factors not previously studied, such as episodic pain and depression, did not predict RT response. As expected, there was no difference in response rates among patients receiving single fraction RT compared to multiple fraction RT. Although single fraction RT is recommended for treatment of uncomplicated bone metastases and several studies have shown similar response rates,[3] only 37% of the patients included in this study received single fraction RT. This is a surprising finding given the available data and the obvious benefit for the patients with single fraction RT and can probably be explained by a lack of implementation of new evidence in clinical practice.

In our study 44 % of the patients responded to RT, which is lower than the average response rate of about 60 % in the latest systematic review by Rich et al.[3] Studies included in the latest systematic reviews reports a wide range of response rates. This probably reflects a variety in design between studies, but also differences in study populations and possible differences in radiation techniques.[3,26,38] The PRAIS study was designed to reflect a real life clinical practice. RT response were calculated according to international consensus and we included both outpatients and patients admitted to hospital. We also chose to include all patients where clinicians had evaluated the patient to be a candidate for RT due to painful bone metastases and did not apply a study specific cut-off concerning the self-reported level of pain. This might have increased the number of non-responders compared to other studies.

In our study 94 patients (16% of enrolled patients) died within 8 weeks after RT administration and this concurs with what is previously reported.[4] The response rate in patients dying between 3 and 8 weeks was only 12 %. RT given towards the end of life may not be beneficial for patients if it causes additional distress due to travelling, treatment planning and administration. RT late in the disease trajectory may be due to the known difficulties in defining a prognosis for advanced cancer patients, but it could be speculated that some patients should have been referred for palliative RT earlier.

The clinical aim of studies identifying predictors for response to palliative RT for bone cancer pain is to stratify patients to receive or not receive RT. This study demonstrates that performance status is one of the most important variables to predict RT response. We found that response rates more than doubled in patients with Karnofsky performance status >80 compared to performances status <50. Patients with a cancer diagnosis of breast or prostate cancer and patients with soft tissue expiation outside bone did also have significantly better response rates, although it is difficult to select patients for RT based on these features alone (Table 3, Fig. 2).

The discriminative ability of the model was higher than in the previously published secondary analysis by Van der Velden who presented a risk score calculation.[4] Still, we chose to not develop a specific predictive score for RT response based on the current findings. In order to be clinically useful a clinical risk score should give a certain cut-off value which reliably discriminate patients, a feature not available in previous studies or in the current study. However, we and others have identified clinical features (Fig. 2) which the clinicians should

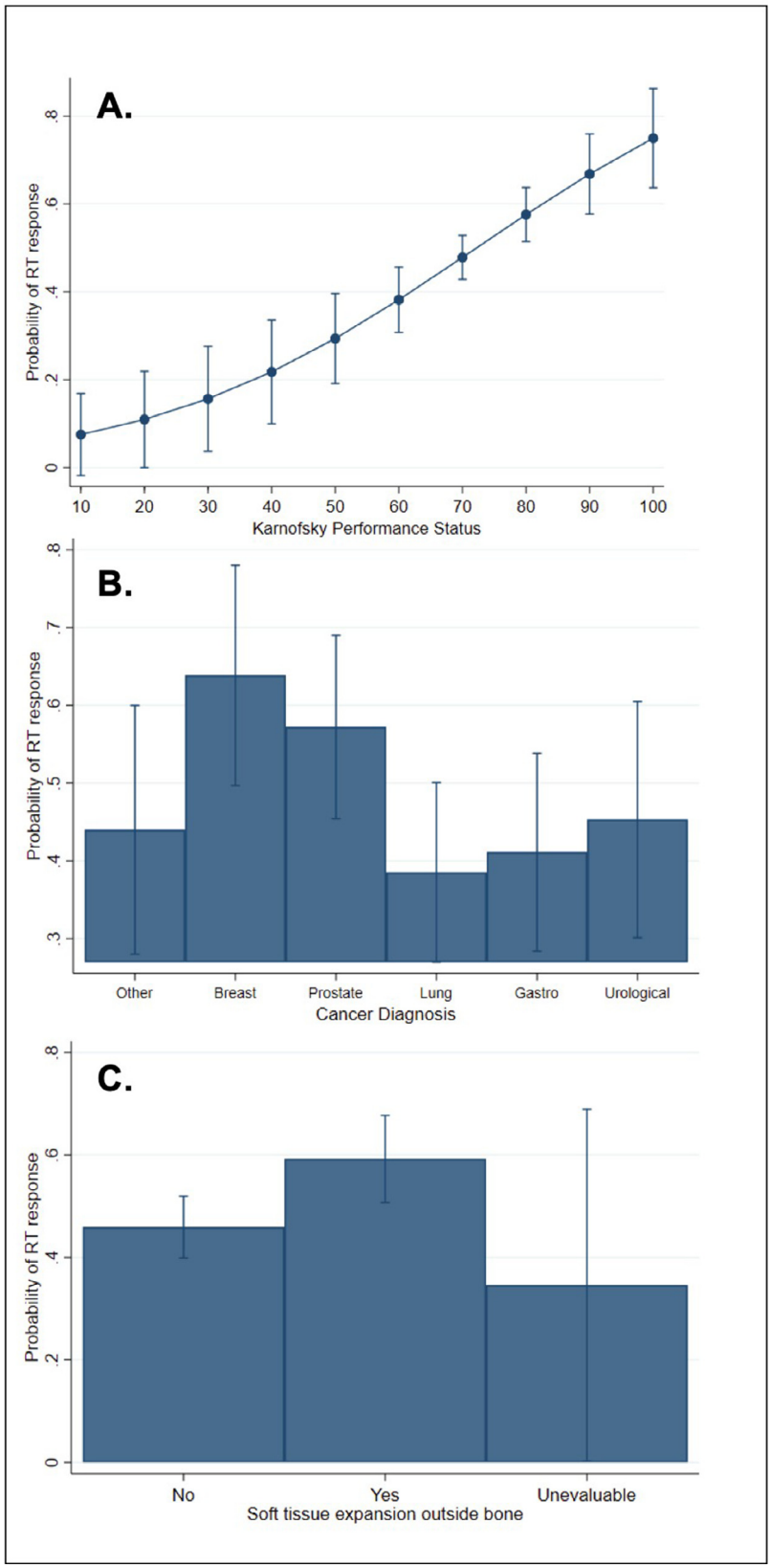

Fig. 2. Predictive probabilities based on the complete case model for A. Karnofsky performance status, B. Cancer diagnosis, C. Soft tissue expansion outside bone. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

take into consideration for RT planning together with other factors such as RT availability, patient preferences, expected adverse effects, travelling distance and to which extent pain can be controlled by analgesics.

This study has strengths and limitations. Strengths of the study are the prospective design, the large patient number, patients included from several study centers, that it was primarily designed to identify predictors of response to palliative RT, that relevant markers for tumor characteristics and inflammation were included, and that the study reflects real life clinical practice. A limitation of the study is that we have not included an analysis from a replication cohort. Second, as expected in a clinical cancer pain study several patients have one or more missing variables and some patients are lost to follow-up due to death or other causes. It is plausible that these patients have a more severe disease or higher symptom burden than patients able to complete the study procedure. However, complete-case, worst-case and best- case sensitivity analyses showed stable values in the different models. Missing variables are a shared issue in research in palliative cancer patients, and the number of missing variables in this study was similar or lower than in the previous multivariate analyses on RT predictors.[4,5] Third, we did not assess the incidence and intensity of short-term adverse effects from RT therapy. Such adverse effects are factors in a risk/benefit assessment. Forth, as in all other studies using the consensus definition for RT response the opioid dose might be increased because of pain in other sites than the irradiated one, introducing a potential bias with regard to RT effect. Finally, the participating centers may not be representative for other treating centers due to local differences in admission, treatment planning and distribution of RT. Most patients were consecutively included in the study, but in three of the participating study centers only a minor part of the treated patients was included, and there was not an even distribution of patients between the four countries.

Conclusion

In conclusion, this prospective, multicenter, clinical study showed that better performance status, breast or prostate cancer and presence of soft tissue expansion outside bone predicted RT response in patients with painful bone metastases. Inflammation measured with CRP was not a predictor for RT response, but patients using corticosteroids had significantly lower response rates.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jpainsymman.2021.03.022.

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