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ORIGINAL ARTICLE

Screening for psychological distress before radiotherapy for painful bone metastases may be useful to identify patients with high levels of distress

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ABSTRACT

Background: Psychological distress (PD) has a major impact on quality of life. We studied the incidence of PD before and after radiotherapy for painful bone metastases. Furthermore, we aimed to identify factors predictive for PD.

Methods: Between 1996 and 1998, the Dutch Bone Metastasis Study included 1157 patients with painful bone metastases. Patients were randomized between two fractionation schedules. The study showed a pain response of 74% in both groups. Patients filled out weekly questionnaires for 13 weeks, then monthly for two years. The questionnaires included a subscale for PD on the Rotterdam Symptom Checklist. We used generalized estimating equations and multivariable logistic regression analyses.

Results: At baseline, 290 patients (27%) had a high level of PD. For the entire group, the level of PD remained constant over time. The majority of patients with a low level of PD at baseline remained at a low level during follow-up. In patients with a high level of PD at baseline, the mean level of PD decreased after treatment and stabilized around the cutoff level. Female patients, higher age, worse performance, lower pain score and worse self-reported QoL were associated with an increased chance of PD, although the model showed moderate discriminative power.

Conclusions: A substantial proportion of patients had a high level of PD before and after radiotherapy for painful bone metastases. Most patients who reported high levels of PD when referred for palliative radiotherapy remained at high levels thereafter. Therefore, screening of PD prior to treatment seems appropriate, in order to select patients requiring intervention.

Introduction

Radiotherapy is an effective treatment for patients with painful bone metastases. The pain response rate is above 60%, with the golden standard of a single fraction of 8 Gray (Gy) [1–3]. Although reduction of pain is the main treatment goal, it is also important to focus on quality of life (QoL) [4]. Painful bone metastases have a negative impact on the QoL of patients [5,6]. Studies show that radiotherapy stabilizes or improves QoL [7–15].

Psychological distress (PD) has a major impact on QoL and is defined as a multi-determined unpleasant emotional experience that may interfere with the ability to cope effectively with cancer, its physical symptoms and treatment [16]. Symptoms such as nervousness, depressed mood, worrying, anxiety and irritability contribute to PD [17] and are quite

common in patients with advanced cancer. Nervousness for example, is experienced by almost 50% of incurable cancer patients, according to a systematic review in 25,074 patients [18]. Other symptoms, such as depressed mood, worrying, anxiety and irritability are reported by 39, 36, 30 and 30% of patients, respectively.

Up to 50% of patients suffer from PD, however only a small percentage of them are referred for intervention [19,20]. Routine screening of distress in patients with disseminated cancer is uncommon [20], despite the fact that several interventions exist which can decrease PD, such as psychosocial interventions [21], cognitive therapy [22] or psycho-educational interventions [23,24]. Some patients disclose the presence of PD to their health care providers spontaneously and are therefore easily identified. Other patients do not communicate or even recognize their PD and its impact. Patients and

health care providers may also be unaware of the possibility of interventions to reduce PD [19]. It is therefore important to identify patients with high levels of PD early, to increase awareness of both patients and health care professionals on this topic and if wanted, to offer interventions. Most of the current literature on PD was acquired in patients with cancer treated with a curative intent [19,24–28]. To our knowledge, no studies were performed so far specifically in patients with bone metastases. No studies reported the extensive course of PD, both in palliative and curative setting.

In earlier publications we showed that total QoL and its separate domains, including the psychosocial domain, diminish towards death [14] and that patients responding to radiotherapy have a better QoL than non-responding patients [29]. The aim of the present analysis was to focus on the incidence of PD in patients with painful bone metastases and its course following palliative radiotherapy. We aimed to identify factors predictive for PD. For this purpose, the data from the randomized Dutch Bone Metastasis Study (DBMS) [1] were used.

Patients and methods

The DBMS was a nationwide, randomized trial in patients with uncomplicated painful bone metastases. Between 1996 and 1998, 1157 patients were randomized between a single fraction of 8 Gy or 24 Gy in six fractions. The mean age was 65 years (range, 32–89 years). Fifty-four percent of the patients were male. Most patients had breast cancer (39%), prostate cancer (23%) or lung cancer (25%). At study inclusion, the mean and median time since diagnosis of the primary tumor was more than three years and almost two years, respectively. The median and mean survivals of the entire group were 30 and 49 weeks, respectively, with a range of 0.3 to 142 weeks. The study showed the equal effectiveness of both treatment schedules with regard to pain response, which was the primary endpoint. All patients provided informed consent and the Medical Ethics Committees of participating institutions approved the study. Further details of the DBMS and the study protocol were published elsewhere [1,30].

Questionnaires

At randomization and during follow-up, patients filled out weekly questionnaires for thirteen weeks and then monthly until two years of follow-up, death or closure of the study in December 1998. The questionnaires were carried out by mail. The questionnaires consisted, amongst others, of the Rotterdam Symptom Checklist (RSCL) [17], a visual analog general health scale (VAS-gh), a pain scale and pain medication intake. The RSCL consists of three subscales (psychological distress, physical symptom distress and activity level impairment) and a scale for overall valuation of life (on a seven-point Likert-type scale, with a low score indicating few or no complaints) (VRS-vl). All other RSCL-items were rated on a four-point Likert-type scale, ranging from 1 (no complaints at all) to 4 (many complaints). Sum scores were calculated conforming to the manual of the RSCL, inserting the

personal scale mean of the patient in cases where less than half of the items of the sum score were missing [17]. At baseline, the score for the RSCL-subscale for PD was available in 94% of patients. In addition to the RSCL scales, a VAS-gh was noted on a line from 0 (no complaints) to 100 (worst general health possible). The advantage of the latter is that each individual patient valuates for himself the impact of his combined physical, psychological and functional condition on their overall perceived general health. Pain was measured using an 10-point numeric rating scale, ranging from 0 (no pain) to 10 (the worst pain imaginable). A pain score of at least 2 was required to enter the study [1].

Psychological distress

The PD subscale of the RSCL consists of seven items, namely irritability, worrying, depressed mood, nervousness, despairing about the future, tension and anxiety. Since all items are scored on a four-point Likert-type scale, the total sum score ranges from 7 (no PD) to 28 (maximum amount of PD) [17]. Ibboston et al. studied the RSCL in 513 cancer patients, in order to screen for anxiety and depression. The RSCL performed well in patients with progressive disease. A cutoff point with good sensitivity and specificity for the presence of PD was determined at 16 [31].

To determine whether patients with an intermediate level of PD at baseline might have more chance of converting to a high level of PD during follow-up, the patients below the cutoff value were divided into two groups: low (7–11) and an intermediate (12–16) level.

Pain response

Pain response was calculated by taking changes in pain score and pain medication into account, according to international criteria [32]. No fixed time interval from the date of randomization was applied. A response was calculated if at least two successive follow-up pain scores were available.

Statistical analyses

Chi-Square tests were used to compare the categorical variables at baseline. To visualize and compare the course of PD over time, we used generalized estimating equations (GEE-measurements), a longitudinal data analysis technique. p values are based on two-sided tests and considered significant if $p < .05$. Figures were created based on the least square means of the repeated measurements.

To assess which variables were predictive for PD at baseline, we dichotomized the patients into having or not having PD (sum score <17 and ≥ 17). We applied multivariable logistic regression analyses to relate candidate predictors for PD. First, a full model was used, including all preselected variables. Subsequently, we eliminated the variables by a backward selection process with a threshold p value of .20, based on likelihood-ratio test results. The chosen p value of .20 intends to limit the loss of information and to also select weaker predictors, although at the cost of including 'noise'

Table 1. Baseline characteristics and level of psychological distress.

Baseline variables n	All patients 1157	PD low (7 to 11) 457	PD intermediate (12 to 16) 337	PD high (17 to 28) 290	PD unknown 73	p value*	Differences between (p value)*
Primary tumor						.016	
Breast	451 (39%)	161 (36%)	129 (38%)	138 (38%)	23 (32%)		Low–intermediate: .414
Prostate	267 (23%)	111 (24%)	87 (26%)	54 (19%)	15 (21%)		Low–high:.008
Lung	287 (25%)	119 (26%)	85 (25%)	59 (20%)	24 (33%)		Intermediate–high : .025
Other	152 (13%)	66 (14%)	36 (11%)	39 (13%)	11 (15%)		
Age						.308	
≤65 years	565 (49%)	218 (48%)	178 (53%)	139 (48%)	30 (41%)		
>65 years	592 (51%)	239 (52%)	159 (47%)	151 (52%)	43 (59%)		
Gender						<.001	
Male	624 (54%)	268 (59%)	189 (56%)	123 (42%)	44 (60%)		Low–intermediate: .471
Female	533 (46%)	189 (41%)	148 (44%)	167 (58%)	29 (40%)		Low–high: <.001
							Intermediate–high: .001
KPS						<.001	
90–100	221 (19%)	97 (21%)	80 (24%)	34 (12%)	10 (14%)		Low–intermediate: .612
70–80	592 (51%)	244 (53%)	169 (50%)	145 (50%)	34 (47%)		Low–high: <.001
20–60	344 (30%)	116 (25%)	88 (26%)	111 (38%)	29 (40%)		Intermediate–high: <.001
Pain score						.497	
2–5	428 (37%)	172 (38%)	123 (37%)	110 (38%)	23 (32%)		
6–7	362 (31%)	144 (32%)	118 (35%)	83 (29%)	17 (23%)		
8–10	367 (32%)	141 (31%)	96 (29%)	97 (33%)	33 (45%)		
VRS-vl[a]						<.001	
1–3	350 (30%)	189 (41%)	92 (27%)	48 (17%)	21 (29%)		Low–intermediate: <.001
4	364 (32%)	152 (33%)	113 (34%)	75 (26%)	24 (33%)		Low–high: <.001
5–7	443 (38%)	116 (25%)	132 (39%)	167 (58%)	28 (38%)		Intermediate–high: <.001
VAS-gh[a]						<.001	
0–33	236 (20%)	127 (28%)	71 (21%)	30 (10%)	8 (11%)		Low–intermediate: .043
34–66	530 (46%)	220 (48%)	164 (49%)	108 (37%)	38 (52%)		Low–high: .001
67–100	391 (34%)	110 (24%)	102 (30%)	152 (52%)	27 (37%)		Intermediate–high: <0.001
Visceral metastases						.904	
No	838 (72%)	331 (72%)	244 (72%)	214 (74%)	49 (67%)		
Yes	319 (28%)	126 (28%)	93 (28%)	76 (26%)	24 (33%)		
Systemic therapy						.205	
No	531 (46%)	215 (46%)	156 (46%)	118 (41%)	42 (57%)		
Yes	626 (54%)	242 (54%)	181 (54%)	172 (59%)	31 (43%)		
Treatment arm						.215	
6 × 4 Gy	578 (50%)	218 (48%)	180 (53%)	138 (48%)	42 (58%)		
1 × 8 Gy	579 (50%)	239 (52%)	157 (47%)	152 (52%)	31 (43%)		
Pain medication						.112	
No opioids	667 (58%)	279 (61%)	200 (59%)	155 (53%)	33 (45%)		
Opioids	490 (42%)	178 (39%)	137 (41%)	135 (47%)	40 (55%)		
Localization of pain						.41	
Extremities	173 (15%)	76 (17%)	45 (13%)	44 (15%)	8 (11%)		
Spinal column	345 (30%)	119 (26%)	109 (32%)	93 (32%)	24 (33%)		
Pelvis	455 (39%)	183 (40%)	134 (40%)	109 (38%)	29 (40%)		
Other	184 (16%)	79 (17%)	49 (15%)	44 (15%)	12 (16%)		

*Pearson Chi-Square.
[a]VRS-vl and VAS-gh: the lower, the better QoL.
KPS: Karnofsky performance score; VRS-vl: verbal rating score, valuation of life; VAS-gh: visual analog score, general health; Gy: gray.

variables [33]. The preselected baseline variables, based on the literature and clinical experience, were primary tumor (breast, prostate, lung or other cancer), age (≤65 or >65 years), gender (male or female), Karnofsky performance status (KPS) [34] (<60, 70–80 or 90–100), baseline pain score (2–5, 6–7 or 8–10), VRS-vl (1–3 (good), 4 or 5–7 (bad)), VAS-gh (0–33 (good), 34–66 or 67–100 (bad)), visceral metastases (yes or no), systemic therapy (yes or no), treatment arm (6 × 4 Gy or 1 × 8 Gy), pain medication (no opioids or opioids), localization of pain (extremities, spinal column, pelvis or other) and time since diagnosis of primary tumor (continuous). To prevent that independent variables entered into the model were correlated with each other, especially those measuring daily living abilities and general health, we checked for multicollinearity.

The database was analyzed using IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) and SAS software (version 9.2, SAS Institute Inc, Cary, NC, USA).

Results

Relation between patient characteristics and PD at baseline

In 1084 (94%) patients, the level of PD at baseline could be calculated. The mean level of PD at baseline was 13.4 for the entire group, with a median of 12.0. Twenty-seven percent of patients had a high level of PD at baseline (score ≥17). Table 1 shows baseline characteristics of the three baseline levels of PD.

The mean age was 65 years (range 32–89 years). Within the different groups of primary cancer, 32% of patients with breast cancer had a high level of distress, compared to 21% of patients with prostate cancer and 22% of lung cancer patients. Twenty percent of male patients experienced a high level of distress, compared to 31% of female patients. There was a significant gender difference in the 285 patients with lung cancer and the fourth group consisting of 145 patients

Table 2. Univariate (UVA) and final multivariate (MVA) logistic regression analyses on potential baseline predictors for high level of psychological distress before palliative radiotherapy for painful bone metastases.

	Odds ratio (95% CI)	
Baseline variables	UVA[c]	MVA[c]
Primary tumor		
Breast	1.00	[a]
Prostate	0.57 (0.40–-0.820)	
Lung	0.61 (0.43–0.87)	
Other	0.80 (0.53–1.22)	
Age		
≤65 years	1.00	1.00
>65 years	1.08 (0.83–1.420)	1.28 (0.95–1.73)
Gender		
Male	1.00	1.00
Female	1.84 (1.40–2.42)	1.94 (1.44–2.62)
KPS		
90–100	1.00	1.00
70–80	1.83 (1.21–2.76)	1.44 (0.92–2.24)
20–60	2.83 (1.84–4.37)	1.67 (1.03–2.70)
Pain score		
2–5	1.00	1.00
6–7	0.85 (0.61–1.18)	0.65 (0.46–0.94)
8–10	1.10 (0.80–1.52)	0.60 (0.42 - 0.87)
VRS-vl[b]		
1–3	1.00	1.00
4	1.66 (1.11–2.47)	1.40 (0.91–2.17)
5–7	3.94 (2.74–5.67)	2.54 (1.63–3.96)
VAS-gh[b]		
0–33	1.00	1.00
34–66	1.86 (1.20–2.88)	1.43 (0.88–2.31)
67–100	4.73 (3.06–7.32)	2.64 (1.55–4.48)
Visceral metastases		
No	1.00	[a]
Yes	0.93 (0.69–1.26)	
Systemic therapy		
No	1.00	[a]
Yes	1.28 (0.97–1.68)	
Treatment arm		
6 × 4 Gy	1.00	[a]
1 × 8 Gy	1.11 (0.85–1.45)	
Pain medication		
No opioids	1.00	[a]
Opioids	1.32 (1.01–1.74)	
Localization of pain		
Extremities	1.00	[a]
Spinal column	1.12 (0.74– 1.71)	
Pelvis	0.95 (0.63–1.42)	
Other	0.95 (0.58–1.54)	
Time since primary tumor		
Continuous	1.00 (1.00–1.00)	[a]

[a]did not remain in the final model.
[b]VAS-gh, VRS-vl: the lower the score, the better QoL.
[c]logistic regression analysis.
KPS: Karnofsky performance score; VRS-vl: verbal rating score, valuation of life; VAS-gh: visual analog score, general health; Gy: gray; 95% CI: 95% confidence interval; UVA: univariate analysis; MVA: multivariate analysis

with other primary tumors and their level of PD at baseline. Thirty-seven percent of these women had a high level of PD, compared to 21% of male patients ($p = .016$).

There were significant differences between the three groups in terms of primary tumor, gender, KPS, VRS-vl and VAS-gh. Patients with a high level of PD at baseline were more likely to have breast cancer, to be female and to have a low KPS. They had lower scores for their overall QoL, rated both visually and verbally. There was no relation between PD at baseline and mean pain score.

Because we expected patients with a short survival to have high levels of PD, we analyzed this group separately; of the 405 patients who died within three months or did not

respond anymore after twelve weeks, 24, 32 and 44% had a high, intermediate or low level of PD at baseline, respectively. There was no significant correlation between PD at baseline and survival.

Prediction of high levels of PD at baseline

In Table 2, the results of multivariate analysis are shown. The final model to predict a high level of PD at baseline included age, gender, KPS, pain score, VRS-vl and VAS-gh. Female patients, higher age, lower performance status, lower pain score and worse self-reported QoL were associated with an increased chance of high levels of PD. The area under the curve of the final model was 0.710, indicating moderate discriminative power. The explained variance was 15.3%.

Course of PD

Figure 1 shows the course of PD over time after treatment. Figure 1(A) shows the entire group of patients, in which the mean score of distress remained more or less constant over time. When excluding the 405 patients who did not return the questionnaires after three months, due to death (65%) or other reasons, possibly representing patients in a worse clinical condition, the course of PD remains similar, although with slightly lower scores (Figure 1(A)). When separating the patients into three groups with low, intermediate and high PD at baseline, Figure 1(B) shows that the course of distress was also rather stable for the low and intermediate group. For patients with a high level of distress at baseline, the mean level decreased in the first weeks after treatment and stabilized around 16 (slightly below the cutoff level). Sixty percent of patients with an initially high level of PD never reached a period of several weeks with PD below the threshold value. Of the patients with low or intermediate PD at baseline, approximately 20% were above the cutoff value of 17 somewhere in the follow-up period. No major differences in the course of distress between the four different primary tumors groups were noticed.

Figure 2 shows the proportion of patients with a high, intermediate or low level of PD. The percentage of patients with a high level of PD decreases slightly over time, but remains substantial during the follow-up.

Discussion

We conclude from our analszes that 27% of patients with advanced cancer referred for palliative radiotherapy for painful bone metastases, have a high level of psychological distress when measured on the Rotterdam Symptom Checklist [17]. Furthermore, we showed that female patients, older patients, those with a bad performance score, lower pain score and a low self-reported QoL are at risk for a high level of PD.

The course of PD following radiotherapy depends mainly on the level of PD at the start of treatment. In patients with high levels of distress at baseline the mean level of PD declined to a level just above the cutoff for having complaints.
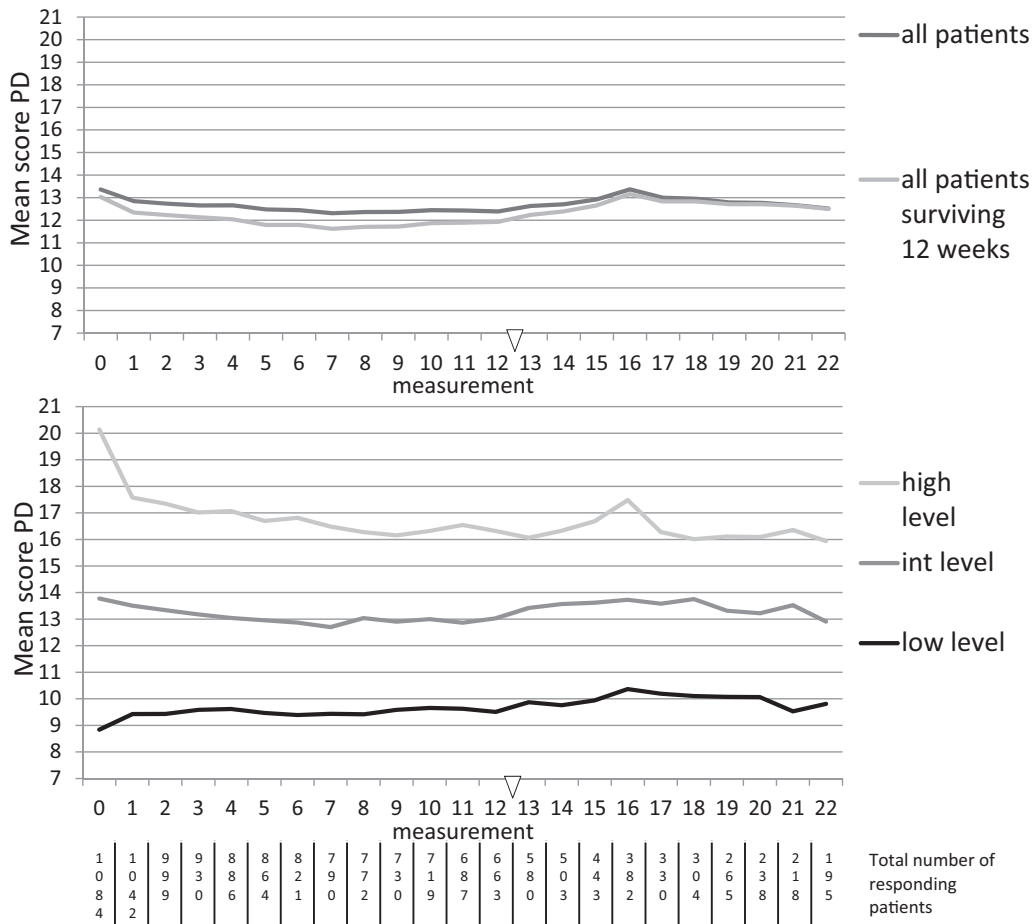
Figure 1. Mean scores of psychological distress (sum score ranges between 7 (low) and 28 (high)) at baseline (measurement 0) and after radiotherapy for painful bone metastases. (A) All patients ($n = 1084$) and all patients who still returned their questionnaires after 12 weeks ($n = 679$). (B) Patients with a high ($n = 290$), intermediate ($n = 337$) and low level ($n = 457$) of psychological distress at baseline. Y-axis: mean scores of psychological distress. X-axis: measurement. The first 12 measurements after baseline were taken weekly and thereafter monthly.

This might be due to (the expectation of) a pain response or the attention of caregivers at the radiotherapy department, even though, 19% of patients experienced high psychological distress a few weeks after treatment. There is little change in the level of distress after treatment in patients with intermediate and low levels of distress at baseline.

The results may be influenced by the loss of follow-up, as three months after treatment only 663 patients (57%) returned questionnaires. This is of course mainly due to the study population of patients with metastasized cancer and a limited life expectancy. Theoretically this might influence the results, since after a few months only the fittest patients remain, who may be less distressed than those patients approaching death. Therefore, in Figure 1(A), we excluded patients with a relatively short survival or those who were lost to follow-up three months after treatment. When excluding those patients, the course of PD remains similar, although this population has a slightly lower level of PD.

The World Health Organization has defined palliative care as 'an approach that improves the QoL of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual' [35]. In patients with advanced cancer, however, both patients and their health care provider are often focused on physical symptoms, with less attention for psychosocial problems. Although PD is a common problem among patients with cancer, many of those patients are not recognized and referred for interventions [19,20]. Several interventions for coping with PD exist, such as individual psychological support, support groups or education programs [20,21,36]. Therefore, screening might be considered. A large recent review concluded that no specific screening tool for distress could be recommended [20]. A screening tool which is often used in Dutch hospitals, the distress thermometer (Lastmeter) [26], uses dichotomized questions such as 'do you feel distressed', supplemented with the amount of distress on a scale from 0 to 10. A review including seven randomized trials showed that screening showed an effect on psychological well-being in four of the seven trials [37]. Furthermore, screening seems to improve communication between health care providers and patients and may enhance psychosocial referrals and facilitate discussions about QoL [20]. However, it is important to be aware that not all patients with a high level of PD want to be referred for an intervention [26]. In a study in 302 cancer patients in
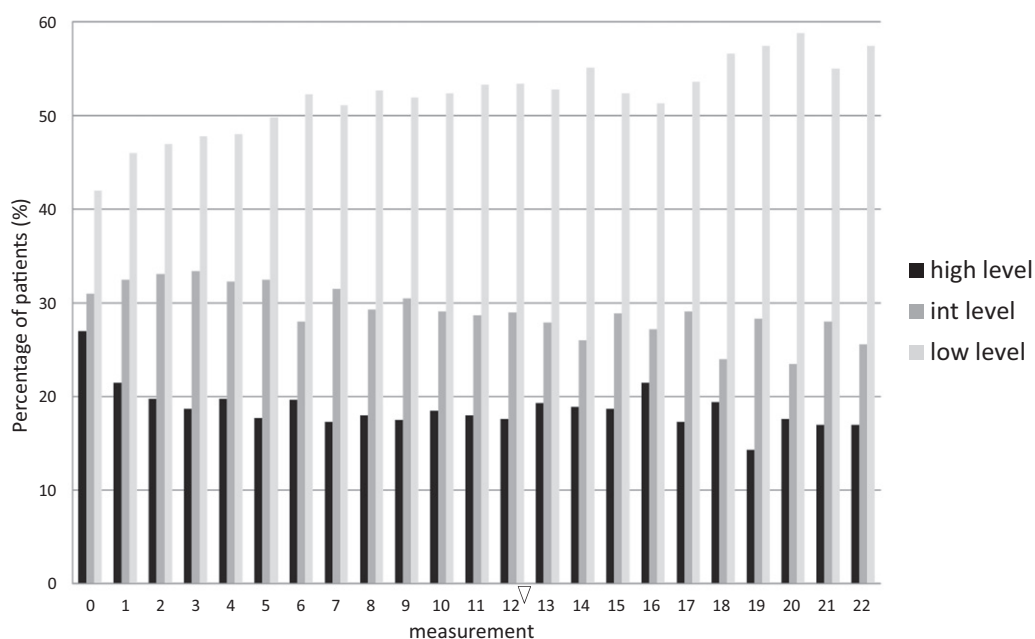
Figure 2. Percentage of patients with a low, intermediate or high level of PD during follow-up. Y-axis: percentage of patients. X-axis: measurement. The first 12 measurements after baseline were taken weekly and thereafter monthly.

the Netherlands, mostly treated with curative intent, 51% of distressed patients did not need an intervention directly after treatment and 25% were already receiving support. After two months, regardless of distress level, 10% of all screened patients reported an unmet need for intervention. The study showed that the need for an intervention was positively related to the level of distress [28]. In a study evaluating 361 referrals for psycho-oncological counseling, 20% of newly referred patients never attended counseling. These patients were mainly men and patients with lung cancer [36]. Therefore, although identification of distress is important in order to identify those patients who might benefit from intervention, referral should be discussed with the individual patient. A study in 1352 Dutch cancer patients found that single patients, patients not living with their partner and patients below 65 years most often wanted an intervention when highly distressed [27]. In Switzerland, a study investigating the barriers and predictors of patients accepting or declining psycho-oncological support has recently opened. The results of this trial should increase the insight into why not all patients with PD want to be referred for an intervention [38].

To our knowledge, no other papers regarding the incidence and course of PD in patients with bone metastases treated with palliative radiotherapy have been published, making it difficult to compare our results with other studies. A Japanese study in 85 patients with advanced non-small cell lung cancer, measured PD at diagnosis, after two and six months, respectively. Forty percent of these patients underwent radiotherapy. They showed that depression and anxiety decreased over time, while other dimensions of PD and the overall level of PD did not. A high level of complaints at baseline predicted for a high level of complaints during follow-up. Therefore, the authors recommended starting an intervention shortly after diagnosis [39]. These findings are

largely in line with our results, although we notice a decrease in overall level of PD in patients with a high level of PD at baseline.

A study among 149 married cancer patients, mainly with advanced disease, showed that female patients reported a higher overall distress than male patients [40]. In the earlier mentioned Dutch study in 302 cancer patients, female patients and younger patients were at higher risk of having a high level of PD [28]. In another paper studying 2776 patients with cancer visiting a tertiary cancer center in Canada, significant gender differences were found; female patients reported depressive symptoms more frequently than male patients and were more likely to receive psychosocial support [19]. Contrary to our results, they also found younger patients to be at a higher risk of PD [19], as did a recent study among breast cancer patients in Morocco [25]. This might be related to the study populations, namely patients with all stages of cancer, where the disruption of social life might be different compared to patients in the palliative phase.

Surprisingly, the three groups of PD had comparable pain scores at baseline. One would expect a higher pain score to be a risk factor for PD, leading to more anxiety, worrying or depression. Accordingly, in a study among 106 palliative patients a higher pain score was correlated with increased distress [41]. In contrast, we found that a lower pain score predicted for a higher level of PD. We have no clear explanation for this finding.

Our data were collected in the late nineties, which might be considered as a limitation of our study, since changes in treatment and subsequent survival may have altered the course of the disease. Nevertheless, it is based on a unique and large cohort of patients with bone metastases. Although the systemic treatment has changed over time, the standard local treatment for patients with painful bone metastases has

remained palliative radiotherapy, with a single fraction of 8 Gy [2]. Therefore, we believe these results are still applicable to current patients with painful bone metastases. Another possible shortcoming could be that we did not study patients with painful bone metastases who did not receive radiotherapy. The course of PD could be a result of progressive disease.

In conclusion, over 25% of patients referred for palliative radiotherapy for painful bone metastases have high levels of PD at baseline, which slightly decreases in the months following treatment. Although palliative radiotherapy is an effective treatment for pain, these patients still experience distress. Therefore, we would like to increase awareness in referring medical specialists and radiation oncologists on the presence of PD. We advise them to screen patients for PD and, if present, to make the topic discussable. If wished for, interventions should be offered, in order to maintain or further improve QoL of their patients.

Disclosure statement

No conflicts of interest declared (for all authors).

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