Received: 5 April 2018 | Revised: 24 January 2019 | Accepted: 14 May 2019

DOI: 10.1111/ecc.13112

ORIGINAL ARTICLE

European Journal of Cancer Care WILEY

No evidence of association between psychological distress and pain relief in patients with bone metastases from castration-resistant prostate cancer treated with 223Radium

Giuseppe De Vincentis[1] | Viviana Frantellizzi[1,2] | Giulia Anna Follacchio[1] | Alessio Farcomeni[3] | Arianna Pani[4] | Riccardo Samaritani[5] | Giovanni Schinzari[6] | Daniele Santini[7] | Enrico Cortesi[1]

[1]Department of Radiological Sciences, Oncology and Anatomical Pathology, Sapienza University of Rome, Rome, Italy

[2]PhD Program: Angio-Cardio-Thoracic Pathophisiology and Imaging, "Sapienza" University of Rome, Rome, Italy

[3]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

[4]Postgraduate School of Clinical Pharmacology, University of Milan "La Statale", Milan, Italy

[5]Oncology Unit, Regina Margherita Hospital, Rome, Italy

[6]Institute of Internal Medicine, Clinical Oncology Unit, Catholic University of Sacred Heart, Rome, Italy

[7]Medical Oncology Department, Campus Bio-Medico University, Rome, Italy

Correspondence
Viviana Frantellizzi, Department of Radiological Sciences, Oncology and Anatomical Pathology, Sapienza University of Rome, Viale Regina Elena 324, 00161, Rome, Italy.
Email: viviana.frantellizzi@uniroma1.it

Funding information
No funding has been received for this paper.

Abstract

Objective: Painful bone metastases cause reduced quality of life (QoL) in patients with castration-resistant prostate cancer (CRPC). Alpha-emitter 223Radium is associated with a clear survival benefit and significant bone pain palliation in CRPC patients with symptomatic bone metastases. The aim of this study was to evaluate the association between pain relief and psychological distress during the time course of therapy in patients treated with 223Radium.

Methods: A total of 63 patients with mCRPC undergoing 223Radium treatment in our Nuclear Medicine Unit, carefully instructed on the possibility of improving the pain and increasing the survival by the treatment, were retrospectively evaluated. Pain response during treatment was assessed with the Brief Pain Inventory Numeric Rating Scale. Psychological distress was evaluated through the analysis of specific items from EORTC QoL questionnaires C30 and BM22, submitted to patients at baseline and after each 223Radium cycle.

Results: Pain intensity showed a significant decrease after first 223Radium administration (−1.03 points, p = 0.0032), with a subsequent stability through the course of treatment (−1.30 points, p = <0.001). Psychological status did not show significant variations during 223Radium treatment, and no association was found between psychological status and pain relief in our population.

Conclusions: In our experience, bone pain palliation provided by 223Radium do not correlate with an improved psychological status in patients with advanced PC. This observation emphasises the role of the psychological aspect in the evaluation of the QoL and the necessity of a multidisciplinary approach in which the emotional aspect of the patient is carefully evaluated.

KEYWORDS

^{223}Ra-dichloride, bone metastases, mCRPC, pain relief, psychological distress, quality of life

1 | INTRODUCTION

Prostate cancer (PC) is the most common male cancer and a leading cause of cancer-related morbidity and death (Siegel, Naishadham, & Jemal, 2013). In PC natural history, approximately 10% of patients will develop a castration-resistant disease, with a median survival of two years (Cookson et al., 2013). The majority of patients with metastatic castration-resistant prostate cancer (mCRPC) has a radiological evidence of bone metastases, which are independently associated with increased mortality (Sathiakumar et al., 2011).

Painful bone causes deteriorated quality of life (QoL) in patients with CRPC. The presence of bone metastases is related to lower performance ability, functional impairment in daily life, risk of developing pathological fractures, spinal cord compression and neurological deficits. Bone pain treatments such as opioids, palliative external beam radiation therapy (EBRT) and orthopaedic surgery could also be related to a negative impact on QoL (Mitchell et al., 2011).

On the psychological side, patients with advanced disease are particularly exposed to depression, anxiety and psychosocial distress. A longitudinal study conducted on PC patients reported that psychological distress, in terms of anxiety and depression, was greatest at diagnosis, with younger patients especially being affected by anxiety (Hinz et al., 2009). Psychological support is felt as one of the greatest care needs by men suffering from PC (Ream et al., 2008). A significant decline in QoL has been reported during the final year of life in patients with mCRPC; however, it is not clear which specific patients' characteristics are associated with a more rapid decline (Melmed, Kwan, Reid, & Litwin, 2002; Sandblom, Carlsson, Sennfält, & Varenhorst, 2004).

Over last years, several novel drugs for CRPC have been introduced, such as the taxan agent cabazitaxel, immunotherapy (sipuleucel-T), RANK-L inhibitor denosumab, androgen biosynthesis inhibitors (abiraterone acetate) and androgen-receptor antagonists (enzalutamide). These antineoplastic agents changed CRPC therapeutic management, significantly affecting the overall prognosis of patients with CRPC. Nevertheless, an appropriate therapeutic sequencing still needs to be defined in order to maximise patient benefit and minimise costs (Frantellizzi et al., 2017; Yin, Hu, & Hartmann, 2013).

In this evolving scenario, the first-in-class alpha-emitter 223Radium has been recently introduced for treatment of CRPC patients with symptomatic bone metastases and no known visceral disease. The efficacy on overall survival (OS) of 223Radium treatment versus placebo in patients with mCRPC has been demonstrated by the results of the international, randomised, double-blind Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) Phase III trial. 223Radium group was characterised by a significant benefit in OS and a delay in time to first symptomatic skeletal event, associated with a relevant bone pain palliation. 223Radium treatment was characterised by a low toxicity profile in terms of both haematologic and non-haematologic adverse events, which were mild to moderate in intensity (Parker et al., 2013).

Thanks to its analogy to calcium, 223Radium targets areas of increased bone turnover such as those surrounding bone metastases and delivering high-energy, short-range alpha particles which are responsible for a local cytotoxic effect due to double-stranded breaks in cell DNA (Bruland, Nilsson, Fisher, & Larsen, 2006; Henriksen, Breistol, Bruland, Fodstad, & Larsen, 2002).

TABLE 1 Baseline patients' characteristics (ECOG = Eastern Cooperative Oncology Group)

Baseline characteristics	Patients (*n* = 63)	%
Age (years)		
Mean (range)	74 (57–90)	
Body Mass Index		
Mean (range)	25.8 (19.6–39.2)	
Time from diagnosis		
Median (years)	7	
Time from pain onset		
Median (years)	2.8	
Gleason Score		
Mean (range)	8 (6–9)	
6	1	1
7	15	24
8	19	30
9	13	21
Unknown	15	24
ECOG performance status		
Mean (range)	1.3 (0–3)	
0	6	9
1	37	59
≥2	20	32
Skeletal burden		
0–6 mets	5	8
6–20 mets	50	80
≥20 mets	8	12
Brief Pain Inventory Pain Score		
Low (0–3)	18	28
Intermediate (4–7)	30	48
Severe (8–10)	15	24
Narcotic Score		
0	18	28.5
1–3	18	28.5
4–8	9	14.5
≥9	18	28.5
Prior docetaxel treatment		
Yes	33	53
No	30	47
Number of previous systemic treatments		
0	14	22
1	21	33
2	16	25
≥3	12	20

This direct cytotoxic effect is held responsible for an increase in PSA values that are not infrequently found during therapy, the so-called "flare phenomenon" (De Vincentis et al., 2016).

Because of alpha particles' short penetration range (<100 μm), there is limited damage to bone marrow (Henriksen, Fisher, Roeske, Bruland, & Larsen, 2003; Hobbs et al., 2012; Li, Russell, & Allen, 2004).

Survival benefit distinguishes 223Radium from other bone-targeted therapies, such as local radiotherapy, radioisotopes ^{89}Sr and ^{153}Sm-EDTMP, zoledronic acid and denosumab, which have demonstrated to be effective on pain palliation but have no impact on OS (Finlay, Mason, & Shelley, 2005).

Since its introduction, 223Radium treatment is gaining widespread use in clinical practice. During recent years, many clinical trials conducted in expanded access setting confirmed the safety and efficacy of this treatment (Morris et al., 2015; Sartor et al., 2016; Vogelzang et al., 2015).

The aim of this study was to evaluate whether pain palliation is associated with an improvement in QoL in patients with mCRPC during 223Radium treatment, with a specific focus on patients' psychological distress. Patient-reported pain measures have become a preferential outcome score in pain assessment; there is, however, scarce information in literature concerning the correlation between pain and psychological status in patients with CRPC undergoing 223Radium therapy.

2 | METHODS

2.1 | Participants

A total of 63 patients with CRPC and symptomatic bone metastases undergoing 223Radium treatment in our Nuclear Medicine Unit were enrolled in the study. Exclusion criteria were the presence of visceral metastases, a malignant lymphadenopathy that was more than 3 cm in the short-axis diameter, Eastern Cooperative Oncology Group (ECOG) performance-status score higher than to 2, active inflammatory bowel disease, concurrent other chemotherapy or biologic therapy for prostate cancer (androgen-ablation therapy was maintained).

A total of 253 223Radium cycles were administered to these patients in a period between July 2015 and June 2016. On average, patients had been diagnosed with prostate cancer for 7 years and median time from bone pain onset was 2.8 years. Baseline patients' characteristics are summarised in Table 1.

2.2 | Procedure

This observational prospective study was approved by the Institutional Review Board (Approval number: 4381- 15/02/17) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients signed a written informed consent. Each patient was carefully informed on the possibilities of improving the pain and increasing the survival by the treatment. Currently, 223Radium therapy consists of six intravenous injections (55 kBq per kg of body weight) administered every 28 days.

2.3 | Measures

During treatment, pain score was evaluated by the means of the 11-points Brief Pain Inventory Numeric Rating Scale (BPI-NRS, where a score of 0 means no pain, 1–3 mild pain, 4–6 moderate pain, 7–8 severe pain and 9–10 very severe pain). A Narcotic Score considering medication type and medication frequency was used to monitor pain medication use during treatment (Tong, Gillick, & Hendrickson, 1982).

Briefly, Narcotic Score was calculated as follows:

$$(\text{medication type}) \times (\text{medication frequency})$$

Medication types were classified as 0: None; 1: Analgesic; 2: Mild narcotic; and 3: Strong narcotic.

Frequency of pain medication administration was defined as 0: None; 1: Less than daily; 2: Once per day; and 3: More frequently than once per day.

To assess QoL endpoints, patients were asked to complete the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the bone metastases module QLQ-BM22. Both questionnaires were submitted to patients at the study site at baseline and after every 223Radium cycle.

EORTC QLQ-C30 version 3.0 is a well-established tool to evaluate general cancer-related aspects of QoL. It is composed of 30 items divided into five Functional Scales (physical, role, emotional, cognitive and social), a Symptom Scale and one Global Scale (Aaronson et al., 1993). EORTC QLQ-BM22 module is designed to supplement EORTC QLQ-C30 by specifically addressing clinical issues influencing QoL in bone-metastatic patients. This module is composed of four scales for the assessment of painful sites and pain characteristics (Symptom Scales), functional interference with everyday activities and psychosocial aspects (Functional Scales) (Chow et al., 2011).

To assess the impact of 223Radium treatment on patients' psychological distress, statistical analysis was focused on items number 21-22-23-24 of the EORTC QLQ-C30 and on the psychosocial dimension of the EORTC QLQ-BM22 Functional Scale (items number 17-18-19-20-21-22).

2.4 | Statistical analysis

Data were expressed as mean ± standard deviation or percentages where appropriate. The psychological distress questionnaire was summarised through principal component analysis. The first principal component score was found to summarise adequately the entire questionnaire and was finally used as a continuous measure of psychological distress. A central issue with this longitudinal analysis is that subjects might be lost at follow-up due to exitus, and the

risk of exitus might be associated with the longitudinal outcome. Consequently, dropout cannot be ignored or simply classified as "Missing at Random" without incurring in a potential bias. To avoid this, we worked with joint models, which avoid bias by simultaneously modelling survival and longitudinal measurements, with their dependence captured by shared subject-specific random effects (Rizopoulos, 2012). Similarly, bias-adjusted Pearson correlation coefficients were computed. Where appropriate, *p*-values were adjusted for multiplicity through Bonferroni correction. A *p*-value <0.05 was deemed as statistically significant. All analyses have been conducted using software R version 3.5.1 (R development core team).

3 | RESULTS

At baseline, all patients completed QoL questionnaires. Completion rate had a decreasing tendency at each subsequent assessment due to treatment discontinuation or death. The mean number of 223Radium administered cycles was four, ranging from one to six. 223Radium treatment was completed in 21 patients. In one patient only, 223Radium course of treatment was discontinued because of disease progression consisting in liver metastases, while 41 patients were still undergoing therapy at the time of analysis.

By analysing the association between baseline pain severity and single patients' characteristics, baseline pain score was not related to the number of bone metastases. No association was found between pain outcome and baseline body mass index. A higher Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at baseline was related to a higher baseline pain severity. Nevertheless, pain response to treatment did not seem to be affected by baseline PS ($p = 0.1624$). Baseline pain score presented an inverse correlation with Gleason Score (GS), resulting higher in patients with low-intermediate GS, whereas in patients with a high GS pain severity tended to be lower at baseline and to decrease during treatment. Figure 1 shows box-plot graphics concerning pain scores from baseline over the course of six 223Radium administrations.

As a general trend, baseline pain severity was significantly reduced after 223Radium treatment (baseline vs. any subsequent time point, −1.22 points, $p < 0.001$). We found a decrease in pain score of −1.43 points from baseline to the end of treatment ($p = 0.0054$). Moreover, pain score showed a significant reduction after the first 223Radium administration (−1.03 points, $p = 0.0032$) and this improvement remained stable from the second administration on (−1.30 points, $p < 0.001$).

With the aim of focusing our study on the relationship between pain relief and psychological status, we obtained a single index score that summarised 10 specific items from EORTC QLQ-C30 and BM22 (Table 2), where higher values were associated with a better emotional status. This was obtained through principal component analysis. This psychological score did not show significant variations during 223Radium treatment ($p = 0.19$, see Figure 2). Nevertheless, a separate analysis of each item revealed a peculiar decreasing trend in QLQ-BM22 items number 21–22 during treatment ($p = 0.006$ and

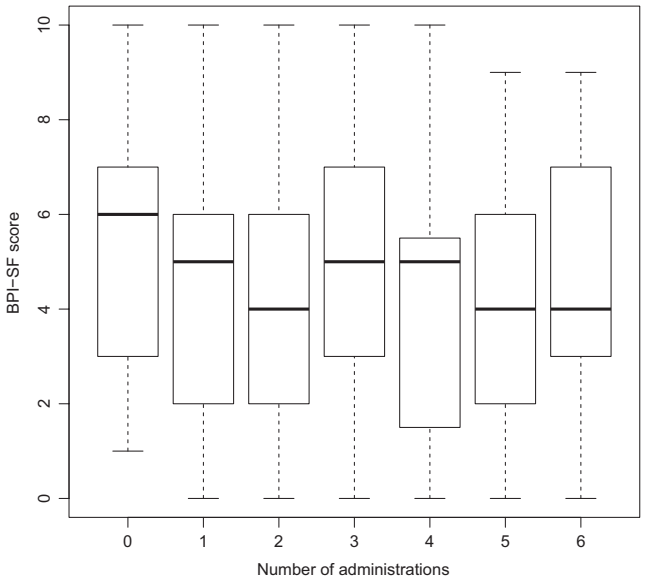

FIGURE 1 Pain response over time

$p < 0.001$ respectively, after Bonferroni correction). In Figures 1 and 2, individuals at each time point are not shown; however, the statistical model we used overrides this apparent bias allowing to examine all the population study.

When accounting for the Narcotic Score, we observed a positive correlation with pain outcome during treatment. In fact, pain increased for every Narcotic Score point (0.21 points for every Narcotic Score point, $p < 0.0001$). This can be easily explained by the fact that our clinical population was not a randomised one, so pain therapy was adjusted to pain severity. After adjusting (at multivariate analysis) by the Narcotic Score, pain showed a decreasing trend over time, with 0.174 points per unit of time ($p = 0.0064$).

Table 3 shows correlation analysis between pain score and psychological status during treatment period.

In general, a higher pain score was generally associated with a worse psychological status; however, after the first 223Radium administration even a high pain score was correlated to an improved psychological status, while statistical correlation between the two variables was lost towards the end of treatment (cycles 5–6).

Examining specifically the correlation between pain score and QLQ-BM22 questions number 21–22, statistical analysis showed a significant correlation between pain score and question number 21 ("hopefulness about pain improvement") for the first half of treatment period, but this relation was no longer valid after the third 223Radium cycle on. No significant association was found between pain and question number 22 ("optimism about personal health status").

4 | DISCUSSION

In our study, 223Radium treatment led to a clinically meaningful improvement in pain outcome. Notably, pain severity was significantly

TABLE 2 EORTC QLQ-C30 and QLQ-BM22 specific items

	Not at all	A little	Quite a bit	Very much
EORTC QLQ-C30				
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
EORTC QLQ-BM22				
17. Have you felt isolated from those close to you (e.g. family, friends)?	1	2	3	4
18. Have you worried about loss of mobility because of your illness?	1	2	3	4
19. Have you worried about becoming dependent on others because of your illness?	1	2	3	4
20. Have you worried about your health in the future?	1	2	3	4
21. Have you felt hopeful your pain will get better?	1	2	3	4
22. Have you felt positive about your health?	1	2	3	4

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; QLQ, Quality of Life Questionnaire.

reduced after the first 223Radium cycle and this improvement remained stable during treatment. Pain outcome was not affected by baseline ECOG PS or by the burden of bone disease. This finding underlines that 223Radium treatment can be useful in either an early or advanced clinical setting. Thanks to the evidences on 223Radium safety, it is common opinion among clinicians that 223Radium treatment should be considered earlier in the therapeutic planning of eligible patients, regardless of previous treatments with docetaxel, abiraterone or enzalutamide (Cornford et al., 2017). Starting treatment with 223Radium as soon as possible, in fact, allows to benefit from the direct cytotoxic effect on cancer cells in bone microenvironment with a minimal toxicity on bone marrow. In this regard, several post hoc safety analyses of patients with ALSYMPCA showed that an early use of 223Radium is associated with a more favourable safety profile (Charalambous & Kouta, 2016).

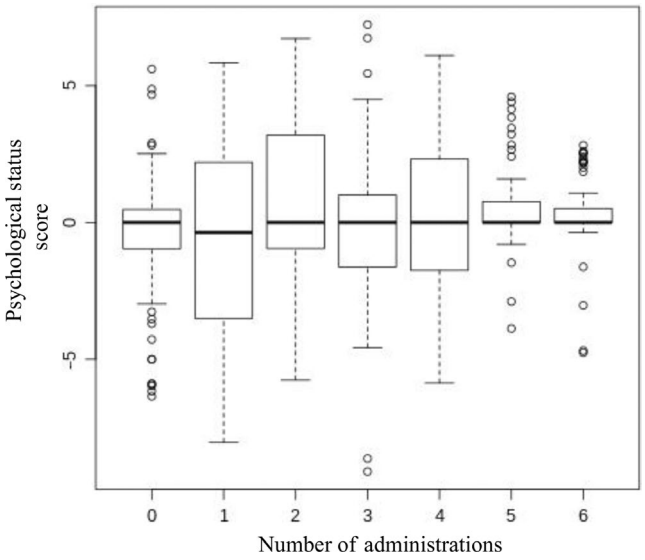

FIGURE 2 First principal component score values by time of psychological status

Cancer-related pain remains a multifactorial, open issue. In fact, the assessment of pain severity is mostly dependent on subjective susceptibility. Therefore, pain burden in the clinical context could vary in dependence to the patient's personal evaluation of "pain" symptom.

In our study, baseline pain score was not related to the number of bone metastases, a result that is consistent with existing literature (Berthold et al., 2008).

In patients with CRPC, bone metastases represent the most common cause of cancer-related pain. Patients with bone-metastatic disease represent a particularly vulnerable group, where the severity of psychological symptoms, such as depression and anxiety, increases with higher levels of pain and functional disability. In comparison to men with non-metastatic or localised PC, those with

TABLE 3 Correlation between pain outcome and psychological status

Time	Baseline	1	2	3	4	5	6
Correlation	−0.30	0.30	−0.54	−0.49	−0.31	−0.08	−0.04
P	0.017	0.020	0.000	0.001	0.055	0.694	0.860

metastatic CRPC report significantly worse QoL owing to pain, fatigue and decreased physical activity (Nilsson et al., 2016).

Recent advances in systemic treatment, associated with an adequate supportive care, have led to a substantial improvement in survival of patients with CRPC. Therefore, an increasing attention is focusing on patient's health-related quality of life (HR-QoL), a subjective multidimensional evaluation that involves functional status, psychosocial well-being, disease-related and treatment-related symptoms. An analysis of this specific outcome in patients with ALSYMPCA demonstrated that 223Radium is associated with significant effects in preserving HR-QoL (Sten Nilsson, 2015). Furthermore, a recent report of the European Society for Medical Oncology (ESMO) rated 223Radium as having the highest level of clinical benefit among new therapeutic treatments for CRPC, as assessed by the means of the validated ESMO Magnitude of Clinical Benefit Scale (Cherny et al., 2015).

It is the authors' opinion that the assessment of the symptomatic benefit deriving from 223Radium treatment should include the numerous factors contributing to well-being status, combining pain assessment to the evaluation of patients' psychosocial domain.

No evidence of association was found between pain response and baseline body mass index. Since the administered activity is calculated according to the patient's weight, this finding shows that pain response may not be influenced by the administered activity. Specific randomised clinical trials are currently evaluating the possibility to rechallenge 223Radium treatment and to modulate protocols with a higher dosage (Sartor et al., 2016).

The inverse correlation found between baseline pain score and Gleason Score represents an intriguing occurrence considering that GS is a well-established prognostic factor for the incidence of bone metastases and that the presence of pain from bone metastases is a recognised predictive factor of the OS in patients with mCRPC (Halabi et al., 2008; Moreira et al., 2016). This issue should be further investigated especially considering that the bone palliation beta-emitting radiopharmaceuticals show no effect on OS and, on the opposite, 223Radium treatment provided a longer OS in subjects who reported no pain with respect to the patients with mild to severe pain at baseline (Saad et al., 2016).

In our series, the comprehensive score used to evaluate psychological status had no significant changes during 223Radium treatment and showed to be remarkably stable for our data. Given the positive trend in pain response, we could expect a different result. A persistent psychological distress despite improvement of pain symptoms could be explained with the particular psychological condition experienced by these oncological patients. Most of patients with CRPC eligible to 223Radium already experienced multiple lines of treatment, and a persistent deterioration in psychological status could reflect the lack of positive expectations towards further therapies, together with a growing anxiety associated with the awareness of the approaching end of life.

Psychological distress in these patients represents a complex condition involving a combination of depression, anxiety, emotional distress related to chronic pain, cognitive fatigue and psychosocial issues concerning family members and caregivers (Sciarra et al., 2018). Even though 223Radium treatment provides a relief of bone pain in most of treated patients, it is evident that this selective achievement cannot contribute to the restoration of psychological well-being. This is the reason why a comprehensive pain management in advanced cancer patients should address equally psychological, social and spiritual aspects of suffering, by providing adequate psycho-oncological support (G. De Vincentis et al., 2018). This assumption is further confirmed by the peculiar trend presented by EORTC QLQ-BM22 items number 21 and 22, evaluating respectively hopefulness about pain relief and optimism about personal health status. Concerning question number 21, the decreasing trend could be explained in opposite ways: either as a stronger feeling of hopelessness about the palliative effect of treatment or as a decline in hope for further pain improvement as a direct consequence of a decrease of pain itself. About question number 22, the decreasing trend is a strong index of patients' decreasing confidence about an improvement of personal health condition.

Statistical analysis of the correlation between pain score and psychological status revealed a particular trend as well, as reported in the Results section. The positive correlation found between the two variables after the first 223Radium administration seems paradoxical, but it could be explained as a result of the strong feelings of hopefulness and expectancy showed by most of our patients at the beginning of this new treatment.

The loss of significance of correlation between pain score and psychological distress towards the end of treatment could be interpreted in a similar way. It was not infrequent, in fact, that patients presented with great expectations about curative effects of this novel treatment. It is evident that, during the course of treatment, patients' consciousness about the advanced stage of the disease grew, together with the awareness that their condition is not susceptible of complete recovery. This opinion is further supported by the similar correlation pattern demonstrated between pain trend and QLQ-BM22 item number 21. A higher pain score, in fact, was related to a stronger feeling of hope for pain improvement during the first half of treatment, while correlation was lost along the second half, suggesting that in the final period of treatment the multiplicity of individual emotive response to pain experience and the attitude of patients can no longer be expressed by a generalised trend.

The lack of significance of correlation between pain outcome and EORTC QLQ-BM22 item number 22, concerning optimism about personal health status, can also be explained on the basis that a good pain response is not necessarily related to a better psychological status.

Purpose of this study was to investigate the correlation between analgesic effects of 223Radium and the psychological and psychosocial conditions of patients suffering for symptomatic bone metastases from CRPC. Our results suggest that bone pain palliation is not linearly associated with an improvement in psychological status of patients in an advanced phase of disease. As a consequence, particular attention should be paid to the patient's and caregivers'

expectations at the time of enrolment, because these are of great impact on the psychological sphere. It is in fact fundamental for them, not to confuse the possibility of palliatives to prolong life with the possibility of increasing the chances of cure. To our knowledge, it is the first study addressed to this aim.

5 | CLINICAL IMPLICATIONS

This study further underlines the need for an accurate assessment of patients' psychological status in the course of therapy, in order to provide the most appropriate, multidisciplinary support against psychological distress, a major issue in patients affected by advanced stage of malignant diseases. In the overall assessment of the QOL, the palliation of the pain symptom may not result in a subsequent impact on the psychological sphere of mCRPC patients. We propose the widespread use of EORTC evaluation questionnaires, since the pain assessment alone does not allow satisfactory examination of the mCRPC patient QoL.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

For this type of study, formal consent is not required.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

RESEARCH INVOLVING HUMAN PARTICIPANTS AND/OR ANIMALS

This article does not contain any studies with animals performed by any of the authors.

ORCID

Viviana Frantellizzi https://orcid.org/0000-0003-3497-4236

REFERENCES

Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., … Takeda, F. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *JNCI Journal of the National Cancer Institute*, *85*(5), 365–376. https://doi.org/10.1093/jnci/85.5.365

Berthold, D. R., Pond, G. R., Roessner, M., de Wit, R., Eisenberger, M., & Tannock, A. I. (2008). Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. *Clinical Cancer Research*, *14*(9), 2763–2767. https://doi.org/10.1158/1078-0432.ccr-07-0944

Bruland, O. S., Nilsson, S., Fisher, D. R., & Larsen, R. H. (2006). High-linear energy transfer irradiation targeted to skeletal metastases by the -Emitter 223Ra: Adjuvant or alternative to conventional modalities? *Clinical Cancer Research*, *12*(20), 6250s–6257s. https://doi.org/10.1158/1078-0432.ccr-06-0841

Charalambous, A., & Kouta, C. (2016). Cancer related fatigue and quality of life in patients with advanced prostate cancer undergoing chemotherapy. *BioMed Research International*, *2016*, 1–11. https://doi.org/10.1155/2016/3989286

Cherny, N. I., Sullivan, R., Dafni, U., Kerst, J. M., Sobrero, A., Zielinski, C., … Piccart, M. J. (2015). A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Annals of Oncology*, *26*(8), 1547–1573. https://doi.org/10.1093/annonc/mdv249

Chow, E., Nguyen, J., Zhang, L., Tseng, L.-M., Hou, M.-F., Fairchild, A., … Bottomley, A. (2011). International field testing of the reliability and validity of the EORTC QLQ-BM22 module to assess health-related quality of life in patients with bone metastases. *Cancer*, *118*(5), 1457–1465. https://doi.org/10.1002/cncr.26410

Cookson, M. S., Roth, B. J., Dahm, P., Engstrom, C., Freedland, S. J., Hussain, M., … Kibel, A. S. (2013). Castration-resistant prostate cancer: AUA guideline. *Journal of Urology*, *190*(2), 429–438. https://doi.org/10.1016/j.juro.2013.05.005

Cornford, P., Bellmunt, J., Bolla, M., Briers, E., De Santis, M., Gross, T., … Mottet, N. (2017). EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. *European Urology*, *71*(4), 630–642. https://doi.org/10.1016/j.eururo.2016.08.002

De Vincentis, G., Follacchio, G. A., Frantellizzi, V., Liberatore, M., Monteleone, F., & Cortesi, E. (2016). Prostate-specific antigen flare phenomenon during 223Ra-dichloride treatment for bone metastatic castration-resistant prostate cancer: A case report. *Clinical Genitourinary Cancer*, *14*(5), e529–e533. https://doi.org/10.1016/j.clgc.2016.04.014

De Vincentis, G., Monari, F., Baldari, S., Salgarello, M., Frantellizzi, V., Salvi, E., … Cortesi, E. (2018). Narrative medicine in metastatic prostate cancer reveals ways to improve patient awareness & quality of care. *Future Oncology*, *14*(27), 2821–2832. https://doi.org/10.2217/fon-2018-0318

Finlay, I. G., Mason, M. D., & Shelley, M. (2005). Radioisotopes for the palliation of metastatic bone cancer: A systematic review. *The Lancet Oncology*, *6*(6), 392–400. https://doi.org/10.1016/s1470-2045(05)70206-0

Frantellizzi, V., Farcomeni, A., Follacchio, G. A., Pacilio, M., Pellegrini, R., Pani, R., & De Vincentis, G. (2017). A 3-variable prognostic score (3-PS) for overall survival prediction in metastatic castration-resistant prostate cancer treated with 223Radium-dichloride. *Annals of Nuclear Medicine*, *32*(2), 142–148. https://doi.org/10.1007/s12149-017-1228-6

Halabi, S., Vogelzang, N. J., Kornblith, A. B., Ou, S.-S., Kantoff, P. W., Dawson, N. A., & Small, E. J. (2008). Pain predicts overall survival in men with metastatic castration-refractory prostate cancer. *Journal of Clinical Oncology*, *26*(15), 2544–2549. https://doi.org/10.1200/jco.2007.15.0367

Henriksen, G., Breistol, K., Bruland, O. S., Fodstad, O., & Larsen, R. H. (2002). Significant antitumor effect from bone-seeking, alpha-particle-emitting (223)Ra demonstrated in an experimental skeletal metastases model. *Cancer Research*, *62*(11), 3120–3125.

Henriksen, G., Fisher, D. R., Roeske, J. C., Bruland, O. S., & Larsen, R. H. (2003). Targeting of osseous sites with alpha-emitting 223Ra:

Comparison with the beta-emitter 89Sr in mice. *Journal of Nuclear Medicine*, *44*(2), 252–259.

Hinz, A., Krauss, O., Stolzenburg, J.-U., Schwalenberg, T., Michalski, D., & Schwarz, R. (2009). Anxiety and depression in patients with prostate cancer and other urogenital cancer: A longitudinal study. *Urologic Oncology: Seminars and Original Investigations*, *27*(4), 367–372. https://doi.org/10.1016/j.urolonc.2008.02.003

Hobbs, R. F., Song, H., Watchman, C. J., Bolch, W. E., Aksnes, A.-K., Ramdahl, T., … Sgouros, G. (2012). A bone marrow toxicity model for223Ra alpha-emitter radiopharmaceutical therapy. *Physics in Medicine and Biology*, *57*(10), 3207–3222. https://doi.org/10.1088/0031-9155/57/10/3207

Li, Y., Russell, P. J., & Allen, B. J. (2004). Targeted α-therapy for control of micrometastatic prostate cancer. *Expert Review of Anticancer Therapy*, *4*(3), 459–468. https://doi.org/10.1586/14737140.4.3.459

Melmed, G. Y., Kwan, L., Reid, K., & Litwin, M. S. (2002). Quality of life at the end of life: Trends in patients with metastatic prostate cancer. *Urology*, *59*(1), 103–109. https://doi.org/10.1016/s0090-4295(01)01457-1

Mitchell, A. J., Chan, M., Bhatti, H., Halton, M., Grassi, L., Johansen, C., & Meader, N. (2011). Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: A meta-analysis of 94 interview-based studies. *The Lancet Oncology*, *12*(2), 160–174. https://doi.org/10.1016/s1470-2045(11)70002-x

Moreira, D. M., Howard, L. E., Sourbeer, K. N., Amarasekara, H. S., Chow, L. C., Cockrell, D. C., … Freedland, S. J. (2016). Predictors of time to metastasis in castration-resistant prostate cancer. *Urology*, *96*, 171–176. https://doi.org/10.1016/j.urology.2016.06.011

Morris, M. J., Sartor, A. O., Vogelzang, N. J., Shore, N. D., Cislo, P., Bangerter, K., & Sweeney, C. (2015). Effect of radium-223 dichloride (Ra-223) on pain from US EAP. *Journal of Clinical Oncology*, *33*(7_suppl), 160–160. https://doi.org/10.1200/jco.2015.33.7_suppl.160

Nilsson, S. (2015). Radium-223 dichloride for the treatment of bone metastatic castration-resistant prostate cancer: An evaluation of its safety. *Expert Opinion on Drug Safety*, *14*(7), 1127–1136. https://doi.org/10.1517/14740338.2015.1045874

Nilsson, S., Cislo, P., Sartor, O., Vogelzang, N. J., Coleman, R. E., O'Sullivan, J. M., … Parker, C. (2016). Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. *Annals of Oncology*, *27*(5), 868–874. https://doi.org/10.1093/annonc/mdw065

Parker, C., Nilsson, S., Heinrich, D., Helle, S. I., O'Sullivan, J. M., Fosså, S. D., … Sartor, O. (2013). Alpha emitter Radium-223 and survival in metastatic prostate cancer. *New England Journal of Medicine*, *369*(3), 213–223. https://doi.org/10.1056/nejmoa1213755

Ream, E., Quennell, A., Fincham, L., Faithfull, S., Khoo, V., Wilson-Barnett, J., & Richardson, A. (2008). Supportive care needs of men living with prostate cancer in England: A survey. *British Journal of Cancer*, *98*(12), 1903–1909. https://doi.org/10.1038/sj.bjc.6604406

Rizopoulos, D. (2012). Joint models for longitudinal and time-to-event data. In *Chapman & Hall/CRC biostatistics series*. Boca Raton, FL: Chapman and Hall/CRC.

Saad, F., Carles, J., Gillessen, S., Heidenreich, A., Heinrich, D., Gratt, J., … O'Sullivan, J. M. (2016). Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: An international, early access, open-label, single-arm phase 3b trial. *The Lancet Oncology*, *17*(9), 1306–1316. https://doi.org/10.1016/s1470-2045(16)30173-5

Sandblom, G., Carlsson, P., Sennfält, K., & Varenhorst, E. (2004). A population-based study of pain and quality of life during the year before death in men with prostate cancer. *British Journal of Cancer*, *90*(6), 1163–1168. https://doi.org/10.1038/sj.bjc.6601654

Sartor, A. O., Heinrich, D., Mariados, N., Méndez-Vidal, M. J., Keizman, D., Thellenberg-Karlsson, C., … Nordquist, L. T. (2016). Radium-223 (Ra-223) re-treatment (Re-tx): First experience from an international, multicenter, prospective study in patients (Pts) with castration-resistant prostate cancer and bone metastases (mCRPC). *Journal of Clinical Oncology*, *34*(2_suppl), 197–197. https://doi.org/10.1200/jco.2016.34.2_suppl.197

Sathiakumar, N., Delzell, E., Morrisey, M. A., Falkson, C., Yong, M., Chia, V., … Kilgore, M. L. (2011). Mortality following bone metastasis and skeletal-related events among men with prostate cancer: A population-based analysis of US Medicare beneficiaries, 1999–2006. *Prostate Cancer and Prostatic Diseases*, *14*(2), 177–183. https://doi.org/10.1038/pcan.2011.7

Sciarra, A., Gentilucci, A., Salciccia, S., Von Heland, M., Ricciuti, G. P., Marzio, V., … Maggi, M. (2018). Psychological and functional effect of different primary treatments for prostate cancer: A comparative prospective analysis. *Urologic Oncology: Seminars and Original Investigations*, *36*(7), 340.e347–340.e321. https://doi.org/10.1016/j.urolonc.2018.03.022

Siegel, R., Naishadham, D., & Jemal, A. (2013). Cancer statistics, 2013. *CA: A Cancer Journal for Clinicians*, *63*(1), 11–30. https://doi.org/10.3322/caac.21166

Tong, D., Gillick, L., & Hendrickson, F. R. (1982). The palliation of symptomatic osseous metastases final results of the study by the radiation therapy oncology group. *Cancer*, *50*(5), 893–899. https://doi.org/10.1002/1097-0142(19820901)50:5<893:aid-cncr2820500515>3.0.co;2-y

Vogelzang, N. J., Fernandez, D. C., Morris, M. J., Iagaru, A., Brown, A., Almeida, F., … Sartor, A. O. (2015). Radium-223 dichloride (Ra-223) in U.S. expanded access program (EAP). *Journal of Clinical Oncology*, *33*(7_suppl), 247–247. https://doi.org/10.1200/jco.2015.33.7_suppl.247

Yin, L., Hu, Q., & Hartmann, R. (2013). Recent progress in pharmaceutical therapies for castration-resistant prostate cancer. *International Journal of Molecular Sciences*, *14*(7), 13958–13978. https://doi.org/10.3390/ijms140713958

How to cite this article: De Vincentis G, Frantellizzi V, Follacchio GA, et al. No evidence of association between psychological distress and pain relief in patients with bone metastases from castration-resistant prostate cancer treated with 223Radium. *Eur J Cancer Care*. 2019;e13112. https://doi.org/10.1111/ecc.13112