JBUON 2019; 24(5): 1747-1760
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

REVIEW ARTICLE

Evaluation of quality of life outcomes following palliative radiotherapy in bone metastases: A literature review

Christina Koufopoulou[1]*, Eftychia Mosa[2]*, Nikolaos Charalampakis[3], Michail Nikolaou[4], Nikolaos Tsoukalas[5], Ioanna Nixon[6], Haytham Hamed Saraireh[7], Jiannis Hajiioannou[8], Dimitrios Kardamakis[9], George Kyrgias[10], Maria Tolia[10]

[1]Faculty of Medicine, School of Health Sciences, University of Thessaly, University Hospital of Larissa, Biopolis, Larisa, Greece; [2]Athens Medical Center, Interventional Radiotherapy-Brachytherapy Unit, Iridium Knife, Marousi, Athens, Greece; [3]Oncology Clinic, H. Dunant Hospital, Athens, Greece; [4]Hippokration University Hospital of Athens, Oncology Clinic, Athens, Greece; [5]Veterans Hospital (NIMTS), Oncology Department, Athens Greece; [6]The Beatson West of Scotland Cancer Center, Glasgow, United Kingdom; [7]Radiation Oncology Department, Jordanian Royal Medical Services, King Hussein Medical Center, Amman, Jordan; [8]Department of Otolaryngology, Faculty of Medicine, School of Health Sciences, University of Thessaly, University Hospital of Larissa, Biopolis, Larissa, Greece; [9]University of Patras, Medical School, Department of Radiation Oncology, Patras, Greece; [10]Department of Radiotherapy/Radiation Oncology, Faculty of Medicine, School of Health Sciences, University of Thessaly, University Hospital of Larissa, Biopolis, Larisa, Greece.

*These authors contributed equally to the study.

Summary

Purpose: *To assess the quality of life (QoL) following palliative radiotherapy (RT) in patients with painful bone metastases.*

Methods: *A literature search limited to English-written publications was carried out, through the Cochrane Central Register of Controlled Trials (November 2018), OvidSP and PubMedCentral (1940-November 2018) databases. Subject headings and keywords included "quality of life"(QoL), "bone metastases", "palliative therapy", "pain" and "radiotherapy". Original articles, literature reviews, trials and meta-analyses revealing alterations in QoL post-RT using ratified measuring tools were examined. Studies referring to other types of metastases (e.g. brain metastases), or to other types of palliative therapy (e.g. the use of bisphosphonates alone), or focusing only on pain, or even reporting QoL only before or only after the use of RT were excluded.*

Results: *Twenty four articles were selected from a total of 1360 articles. Seven trials proceeded to patients' randomization. The most commonly used tool to evaluate QoL was EORTC, followed by Brief Pain Inventory (BPI) and Edmonton Symptom Assessment System (ESAS) questionnaires. All studies showed improvement in symptoms and functional interference scores after RT. The QoL between responders (Rs) and non-responders (NRs) has been juxtaposed in 10 studies. Rs had a significant benefit in QoL in comparison with the NRs.*

Conclusion: *Palliative radiotherapy in painful bone metastases improves responders' (Rs) QoL.*

Key words: *quality of life, bone metastases, palliative therapy, pain, radiotherapy*

Introduction

Bones are among the three most prevalent sites of metastatic disease, along with the liver and the lungs [1]. Regarding the most common neoplasms such as prostate and breast cancer, 7 out of 10 patients may develop bone metastases (BM) [2]. The most usual causative factors of cancer-related

Corresponding author: Tolia Maria, MD. University of Thessaly, School of Health Sciences, Faculty of Medicine, Department of Radiotherapy, Biopolis, 41110, Larissa, Greece.
Tel: +30 6945472195, +30 2413502054, Email: mariatolia@med.uth.gr
Received: 17/01/2019; Accepted: 29/02/2019

pain are metastases in skull, spine, ribs, sternum, pelvis, or extremities [3]. These lesions are also responsible for pathological fractures, spinal cord compression [4] and hypercalcemia, which have a devastating impact on patients' mobility, temper, functional autonomy and social life. Therefore, a dramatic deterioration in patients' QoL is attributed to skeletal metastases, apart from reduced survival and increased morbidity rates [5].

The symptomatic treatment of osseous metastases needs a multidisciplinary approach. Opioids, NSAIDs and corticosteroids are still the first-line pharmaceuticals prescribed for the alleviation of pain. Corticosteroids in particular, are also used to prevent spinal cord compression as a result of a spinal cord metastasis. Additionally, bisphosphonates and denosumab, known as Bone-Targeted Agents (BTAs), are prescribed in order to limit the incidence of skeletal-related events (SREs) and hypercalcemia, while in the same time they moderate the pain induced by bone lesions. Furthermore, radionuclides (i.e., Sr^{89} and Sm^{153}) and hormonal therapy – mostly in breast and prostate cancers – are also applied. Moreover, antiepileptic drugs and other adjuvant pharmaceuticals are also frequently recruited to face the debilitating consequences of metastatic malignancies [6-9]. Surgical decompression and stabilization of the spinal cord (e.g. vertebroplasty/ kyphoplasty) is frequently used when cancer has spread on the vertebrae, while irradiation can prevent pathological fractures and neural compression. Palliation of pain can also be achieved with percutaneous radiofrequency, microwave or cryoablation [8-12].

It is well established that external beam radiation therapy (EBRT) is still the gold standard method for the palliative treatment of painful osseous metastases. Numerous studies hold proof of the cost-effectiveness, time-efficiency and the relatively safe-profile that this technique features. Short courses of RT (i.e 5 fractions of 4 Gy or a single 8 Gy fraction) can significantly improve the quality of life, even in patients with a narrow life-expectancy, since remission of pain and neurological symptoms can be observed within the first few weeks to months, diminishing the need for analgesics and other interventions. Regardless of their location, the use of RT can provide pain-relief in most of the uncomplicated BMs cases. For decades, radiation oncologists worldwide have been using single (SF) or multiple fraction (MF) EBRT with equivalent outcomes in pain relief. Stereotactic body RT is an emerging technique increasingly utilized for the treatment of uncomplicated BMs, however not enough evidence exists supporting its advantage over conventional RT [12-25].

Furthermore, re-irradiation of metastatic lesions is an option that provides satisfying analgesic results, while at the same time it is not accompanied by increased toxicity rates. Stereotactic body RT is a technique that can be used even when the patients have undergone RT in the past, because in this particular method the irradiated field is very small, permitting maximal protection of the organs at risk and the surrounding healthy tissues, while at the same time it provides large fractions of RT in the lesion.

QoL is a concept difficult to understand; an immense variety of factors and a great deal of subjectivity are involved, making its designation and evaluation a complex quest for physicians. Baseline and breakthrough pain, symptoms of spinal cord compression, neural entrapment and hypercalcemia, repeated hospitalizations, adverse effects of the treatments - even the palliative ones - that patients undergo, along with the imminent threat of death they face every moment, challenge palliative medicine's ability to preserve a high QoL in metastatic bone disease. The question of whether pain relief is significantly related with an improvement in QoL has been examined by numerous researchers. So far, literature concludes that better QoL has been reported by patients with uncomplicated BMs whose pain after palliative RT had regressed [22-29].

Several questionnaires have been developed in the attempt to evaluate Health-Related QoL (HRQoL). The questionnaires clinical doctors most regularly apply are the Brief Pain Inventory (BPI) [22,30-33], the European Organisation's for Research and Treatment of Cancer QLQ-C30, C15-PAL (C30's shortened version) and the BM22 (a variation intended specifically for patients with Bone Metastases) [18,20,27,34-41] and the Edmonton Symptom Assessment System (ESAS) [42-44].

BPI evaluates to what extent pain affects the ability of a patient to walk, sleep, work, or do daily activities. It studies the change of mood and social interactions and the feeling of life satisfaction. At the same time BPI assesses the worst, average, and current intensity of the concrete pain.

EORTC's questionnaires are widely used by physicians in order to evaluate patients' functional autonomy, mood and feel-at-ease, while BM22 focuses more on pain and its interference. In ESAS, the severity of pain, tiredness, nausea, depression, anxiety, drowsiness, anorexia, well-being, and shortness of breath at the time of assessment are being rated from 0 (absent) to 10 (worst possible severity) [20,21,45,46].

The purpose of this review was to examine whether there was a significant improvement in

patients' QoL after undergoing EBRT for the palliation of painful metastatic lesions on their bones.

Methods

An elaborate research of the existing literature has been made for that reason. The influence of pain relief on each QoL parameter and to what extent they improved, along with the differences between Rs and NRs were examined and are reported in our review.

A search in medical literature, limited to English-written publications, was carried out through the Cochrane Central Register of Controlled Trials (November 2018), OvidSP and PubMedCentral (1940-November 2018) databases.

The search keywords used in the three aforementioned databases were the following: "quality of life", "bone metastases", "palliative therapy", "pain" and "radiotherapy".

Original articles, literature reviews, trials and meta-analyses revealing alterations in QoL post-RT using ratified measuring tools were included.

Articles and literature reviews either referring solely to other types of metastases (e.g. brain metastases) or solely to other types of palliative therapy (e.g. the use of bisphosphonates alone), or focusing only on pain, or

Table 1. Trials using the EORTC questionnaires

Authors, [publication], year	*Enrollment period*	*Population*	*Follow-up time*	*Inclusion criteria*
Lee et al [35], 2005	1996-2002	Patients with BMs undergoing palliative RT N=31	Months 1 and 3 post-RT	-pathologically confirmed diagnosis of RCC and ≥1 symptomatic site of metastasis -ECOG ≥3 and a life expectancy of ≥3 months
Miszczyk et al [34], 2008	May 2001-Sep 2006	Patients with painful BMs undergoing HBI N=95	Monthly for one year post-RT	-No systemic treatment directly before HBI or during follow-up -PLTs≥ 100,000/mm^3, WBCs≥ 3000/mm^3, HGB ≥8.5 g%
Caissie et al. [20], 2012	Oct 2007-Jul 2010	Patients with BMs under RT N=178	Months 3 and 6 post-RT	-patients with symptoms of the nervous system due to BMs were excluded
Zeng et al. [27], 2012	Mar 2010-Jan 2011	Patients with BMs under RT N=54	1 month post-RT	Not specified
Lam et al. [36], 2013	Mar 2010-Jan 2011	Patients with BMs under RT N=350	1 month post-RT	Not specified
Rief et al. [37], 2014	Sep 2011-Mar 2013	Patients with painful spinal BMs referred for palliative RT N=60(total)	Months 3 and 6 post-RT	-Pts 18-80 y.o -KPS≥70 and -Already under bisphosphonate therapy
Tolia et al. [39], 2014	Not stated	Patients with BMs and depression N=43	Weeks 6-8 post-RT	-Pts 18-80 y.o -Pathologically confirmed CA and rad-confirmed BMs -Confirmed depression -KPS ≥60 and adequate renal and hepatic function
Arias et al. [38], 2015	Jan 2011-Nov 2012	Advanced CA patients with BMs under palliative RT N=75	1 month post-RT	Not specified
Raman et al. [40], 2016	May 2011-Dec 2014 (NCIC SC 23)	Patients from 23 Canadian cancer centers treated with SFRT (8Gy) with pain provoked by BMs	Day 10 and day 42 after RT	-Pts ≥18 y.o -Proven Cancer diagnosis and -Pain corresponding to sites of radiologically confirmed BMs
McDonald et al. [18], 2017		(Prospective phase III randomized controlled trial) N=204		Pain score ≥ 2 on a scale of 0 to 10
Mendez et al. [41], 2017	Sep 2014-Oct 2015	Patients with painful BMs undergoing palliative radio-/chemotherapy N=33	Month 2 after radiation	-Pain score ≥5 -KPS ≥70

Table 2. Changes from baseline to week 4 on a 100-point linear scale using EORTC QLQ-C30 and QLQ-C15-PAL

x	*Miszczyk et al. [34]*	*Caissie et al. [20]*	*Zeng et al. [27]*	*Lam et al. [36]*	*Arias et al. [38]*	*Tolia et al. [39]*	*Raman et al. [40]*	*McDonald et al. [18]*	*Mendez et al. [41]*
PA	18	34	40.9	6.6	34.2	50.3	23	30.1	NS
CO	10	33	NS	3.7	8.9	NS	NS	8,5	NS
PF	7	13	16.7	1,7	8.1	53	13.2	6.2	29
AP	3	33	NS	NS	11.3	46.6	15.7	4.6	NS
SL	5	33	NS	6	19.4	46.6	NS	NS	NS
GHS	7	NS	16.7	3.5	6.6	66.7	NS	10.3	NS
FA	5	5	NS	NS	NS	47.9	15.6	7.5	NS
EF	2	16	NS	2.7	12.7	50.75	18.2	12.3	NS
RF	2	NS	20.5	NS	NS	52.7	NS	NS	NS
DY	2	NS	NS	NS	8.5	51	NS	NS	NS
FI	2	NS	NS	2.6	NS	41	NS	NS	NS
NV	2	NS	NS	NS	NS	NS	13.4	NS	NS
CF	6	NS	NS	NS	NS	50.5	NS	NS	NS
SF	6	NS	NS	NS	NS	46.3	NS	NS	NS

*Tolia [39], Raman [40] and McDonald [18] week 6 and Mendez [41] month 2.

PA=pain, CO=constipation, PF=physical functioning, AP=anorexia, SL=insomnia, GHS=global health scale, FA= fatigue, EF= emotional functioning, RF=role functioning, DY=dyspnoea, FI=financial issues, NV=nausea/vomiting, CF= cognitive functioning, SF=social functioning. NS: not statistically significant.

Table 3. Changes from baseline in the QLQ-BM22 items in week 6 on a 100-point linear scale

	*Zeng et al. [27]**	*Raman et al. [40]*	*Mendez et al. [41]*	*McDonald et al. [18]*	*Rief et al. [37]* (control)-(intervention)	
Pain characteristics	36.4	25.1	33	21.4	12.89	22.37
Functional interference	30.9	23.7	25	18.8	10.58	19.81
Pain site	22.7	15.8	20	13.5	3.8	10.18
Psychosocial aspects	NS	11.2	NS	6.2	3.04	23.7

* Zeng [27] in month 1, Rief [48] in month 3

even reporting QoL only before or only after the use of RT were excluded.

Article titles and abstracts in which the initial research resulted were scrutinized by the main author who then tracked among them those which could presumably suit the aims of this review.

Furthermore, the articles were procured for meticulous inspection and evaluation of their contiguity.

Results

The literature search provided 1360 articles. Among these, only 24 were in accordance with our criteria and they were published between 1977 and 2018 [18,20,22,27,30-44,47-51]. Most of the studies intervened solely by distributing the questionnaire, while only 7 trials proceeded to patients' randomization [18,37,40,47,49-51]. The EORTC questionnaires were applied in a total of 11 trials [18,20,27,34-41] in order to assess QoL, while the next most prevalent tools among authors were the BPI and the ESAS questionnaires, which were used in 5 [22,30-33] and 3 [42-44] studies, respectively. Apart from these, numerous other scales were used by researchers: the McGill–Melzalk Score [36], the Wong-Baker Faces Pain Scale [39], the Hamilton Scale for the evaluation of anxiety and depression in patients (HAM-D) [39], the Spitzer scale [47], the Visual Analog general health Scale (VAS-gh) [48,51], net pain relief [50], the Rotterdam Symptom Checklist [51], and others. The QoL of Rs and NRs have been juxtaposed in 10 of the examined studies [18,20,22,27,30,31,33,35,41,51], according to the International Bone Metastases Consensus' (IBMC) guidelines for the International Pain Response Criteria (IPRC) [52], while no discriminations between the two patient groups were made in the remaining 14 [32,34,36-40,42-44,47-50].

The influence of pain relief on each QoL parameter and to what extent they improved along with the differences between Rs and NRs were examined and are reported in our review.

Discussion

I. The EORTC QoL questionnaires

Eleven of the studies examined in our review were based on completing RTOG EORTC questionnaires; the QLQ-C30 and the QLQ-BM22 were each used in 5 studies, while the QLQ-C15-PAL in 4 (Tables 1-3). It is noteworthy that in the last four-year period an increased tendency among authors in using the BM-specified module can be observed, taking into consideration the previously published review of McDonald et al according to which only one had used the QLQ-BM22 [24].

Lee et al [35] studied pain response and QoL in patients with metastatic renal cell carcinoma. In this trial, patients who had undergone RT for painful bone metastases showed a significant improvement in QoL (>10% score change) at 33%, while 46% and 21% claimed that their QoL deteriorated or showed no significant change, respectively. Fatigue (FA) was the most prevalent QoL parameter improving among responding patients, together with role (RF) and physical (PF) functioning (57%, 52% and 48%, respectively), followed by pain regression and Global Health Status (GHS) that changed significantly in 33% of patients and finally, emotional functioning (EF-26%) and nausea/vomiting (NV-22% of patients)[35].

Miszczyk et al [34] used the QLQ-C30 in order to evaluate patients under treatment with half-body irradiation (HBI) for painful bone metastases. The study demonstrated that a month after treatment, pain regressed by 18 points (linear transformation to the 100-point scale), while physical, role, emotional, cognitive and social function scales, global QoL and all symptom items- apart from diarrhea (DI) and financial issues (FI)- significantly ameliorated. Among all parameters, constipation was the one reaping the greatest benefit from pain subsiding after RT, with physical, social and cognitive functioning followed by GHS being the next greater improvement. Fatigue, insomnia and appetite loss also got substantially better, while role functioning, emotional functioning and nausea/vomiting were the parameters with the smallest - still statistically significant - change from baseline [34].

Additionally, Lam et al [36], using the QLQ-C30 found a significant improvement in 7 HRQoL parameters in advanced cancer patients with BMs: pain and insomnia had a 6,6 and 6-points change from baseline respectively 4 weeks post-RT, while constipation, Global Health Scale (GHS), emotional functioning and financial problems marked a lesser alteration in their scores (3.7, 3.5, 2.7 and 2.6 points respectively) and finally, physical functioning was the least improving symptom (1.5 points). However, the omission of patients' analgesic intake records and the lack of comparison between Rs and NRs pose a difficulty in interpreting their study's results [36].

Tolia et al [38] conducted a prospective trial effect of escitalopram in pain relief and improvement of QoL in depressed patients with BMs that underwent palliative RT. In this study 43 patients received 30Gy of RT in 10 fractions with a simultaneous administration of 20 mg of escitalopram per os, daily. Those individuals were evaluated at baseline and 6 and 8 weeks after treatment was completed, using the QLQ-C30 (v 3.0), the Wong-Baker Faces Pain Scale and the Hamilton Scale (HAM-D). To assess the response to RT, CT or MRI was necessary, while response to the combination of RT and escitalopram was measured through pain relief. All patients had clinical pain relief with a 9.3% of patients experiencing CR and 90.7% PR, according to the IPRC definitions [38].

However, what appears to be quite impressive in this study is the fact that every single parameter of QoL- apart from constipation, diarrhea, nausea/vomiting- marked an immense improvement in patients responding to this combination therapy. In just 6 weeks from baseline, all parameters noted a change of at least 41 up to 66.7 points on the 100-point scale. As far as the Hamilton scale items were concerned [39], significant differences from baseline were reported. Pain subsided significantly, with a change of the mean Wong-Baker score before and after treatment from 4.33 to 0.98. The outcomes of this study demonstrate that escitalopram seems to have a substantial clinical benefit on pain [39], especially when pain inhibitory mechanisms of the central nervous system are involved. Global QoL was the item with the greatest improvement of all, however changes from baseline in both symptoms and functional scales did not show any major differences; financial problems, however, was the parameter improving the least. This study might indicate that, RT when combined with an anti-depressant and pain-modulatory agent, such as escitalopram, can remarkably benefit patients' QoL.

The QLQ-C15-PAL was used by Caissie et al [20] to assess improvements in the QoL of 178 patients with symptomatic BMs after palliative irradiation. Among the patients, 45% of them reported a CR or PR (according to the International Consensus Criteria) in the first week, 62% in the

second week and a month later, and 65% in the second month post-RT [16]. On the one hand, one month after treatment, pain rates demonstrated a 34-point regression in the 100-point scale, accompanied by a 33-point change in each of the following items: constipation, insomnia and appetite loss. Emotional and physical functioning showed a 16 and 13-point change from baseline within the first month, while fatigue was the last item marking a statistically significant positive change (5/100). On the other hand, NRs reported no improvement from baseline neither in symptom and functioning scales nor in overall QoL [20].

Another trial published by Arias et al [38], accrued 75 patients with BMs referred for palliative RT to the Complejo Hospitalario de Navarra in Spain between January 2011 and November 2012. All of them completed the EORTC-QLQ-C15PAL on the first day of treatment and one month after it was over. No information on analgesics consumption was provided and no differentiations between Rs and NRs were made. The study concluded that global QoL was considerably determined by pain intensity [38]. No QoL symptom deteriorated after one month of RT. Additionally, mean pain scores demonstrated a big difference (>20), while insomnia, emotional functioning and appetite loss marked moderate changes from baseline. In the fields of constipation, physical functioning, dyspnoea and global health scale a lesser but still statistically significant improvement was noted (Table 2).

Zeng et al [27] applied both the QLQ-C30 and the QLQ-BM22 to 59 patients who filled in monthly - for a 6-month period following RT- data concerning their HRQoL. Results showed that 37% of them reported a partial response according to the IPRC52, 13.5% experienced pain progression, and 49% were classified as having an indeterminate response. As far as C30's parameters were concerned, pain subsided by 40 points in the 100-point scale, while role and physical functioning significantly improved within 4 weeks from baseline in Rs. The other items of this questionnaire did not show any statistically significant alteration [27]. In studies using the QLQ-BM22 questionnaire, a clear pattern can be observed in response to RT (Table 3).

In Zeng's et al study [27] painful characteristics, functional interference and painful sites scores changed by 36.4, 30.9 and 22.7 points respectively in Rs the first month after RT when compared to NRs. Changes in psycho-social aspects were unexceptional.

The same tendency can be seen in the results of the prospective trial conducted by Mendez et al [41] using both the EORTC-QLQ-C30 and the -BM22 questionnaires (Table 2). According to the IPRC, 25 out of 33 patients had a PR or CR to pain. Among the parameters examined in C30, pain regression was the only parameter that was statistically significant 2 months after radiation in responding patients. Even though this study's sample was modest, the QLQ-BM22 managed to designate the statistically significant differences in most QoL factors, emphasizing its sensitivity.

Rief et al [37] evaluated patients with histologically confirmed spinal metastases of any primary in their randomized, controlled trial, using the EORTC-QLQ- BM22, -FA13 and FBK-R10 questionnaires at baseline, 3 and 6 months from the beginning of palliative treatment. In order to examine the profit of isometric exercises aiming to invigorate paravertebral muscles in patients with spinal BMs, Rief randomized them in two equal groups of 30 patients each: Both arms were undergoing palliative RT regime, while the intervention group was performing these exercises, and the control one followed a conventional physiotherapy program. Both the intervention and the control group experienced statistically significant improvement in all BM22 scales.

Moreover, quite noteworthy is the fact that in both groups, 3 months after treatment, a trend in the changes from baseline in each item can be observed, similar to the outcomes of Zeng et al [27] and Mendez et al [41]: pain characteristics noted a greater alteration in mean score comparing to functional interference, which in its turn exhibited a greater benefit after treatment than the pain sites item. However, contrasting to the control where the psychosocial aspects mean score changed the least from baseline, in the intervention group we can see that this item was the most benefited in these 3 months after the course of combined treatment. Further analysis of patients' scores in each separate query, from the third month post treatment, showed that patients from the intervention group seemed to worry less about the possibility of losing their ability to move and depending on others [37].

Among the parameters assessed by QLQ-FA13, physical fatigue and interference with daily life statistically abated after 6 months in the intervention group - while both worsened in the control group during this time. As far as social sequelae, emotional and cognitive fatigue are concerned, no statistically significant changes from baseline were observed in either of the two groups within 6 months after treatment. Finally, according to the outcomes, emotional distress resulting from the completion of the FBK-R10 also significantly improved in the intervention group 6 months post-RT [37].

Raman et al [40] and McDonald et al [18], prospectively analyzed the QoL of 204 patients participating in NCIC SC 23, a Canadian phase III randomized control trial which examined the efficacy of dexamethasone for pain flare in patients receiving palliative RT for painful BMs. Both studies applied the EORTC-QLQ-C15 and BM22 questionnaires at baseline, 10 and 42 days after treatment was completed.

Raman et al [40] divided patients into improved, stable and deteriorated according to changes reported in overall QoL subscale (≥by 10/100 points). Among QLQ-C30 items in this study, pain marked the highest change in mean score from baseline (23 points), while emotional functioning (18.2), insomnia (15.7), global health scale (15.6), nausea/vomiting and physical functioning demonstrated lesser alterations, albeit substantial, in patients with improved QoL. Cognitive and social function scales, global health scale, insomnia, dyspnoea, diarrhea and financial issues showed no statistically significant differences between baseline and 42-day follow-up [40].

McDonald et al [18] also recorded patients' worst pain score and daily opioid analgesic intake at baseline, days 1 to 10 and day 42 post RT, along with the questionnaire results. Patients with CR and PR according to the IPRC [36] were considered Rs, while changes greater than 10 points from baseline were defined as clinically meaningful. The results showed that 58.8% of the patients responded on day 10 and 38.9% of the patients on day 42. A higher probability of achieving pain response was observed in prostate cancer patients, while among patients without follow-up data on day 42, lung primary and a lower KPS were significantly more prevalent. Rs and NRs were compared at baseline, day 10 and day 42 after RT. Statistically significant improvement was evident in Rs from day 10 in pain, painful characteristics, functional interference, psychosocial aspects and constipation. Rs had significantly greater changes from baseline to day 42 when compared to NRs in pain (improved by 30.1 points), emotional functioning (by 12.3), global health scale (by 10.3) and physical functioning (by 6.2 points) amongst QLQ-C15-PAL parameters. The symptoms assessed in this trial also seemed to abate, with a mean reduction of fatigue by 7.5 points (in contrast to a 9.5-point increase in NRs), of constipation by 8.5 points (while NRs reported a 4.4-point increase) and of anorexia by 4.6 (increased by 5.9 points in NRs) [18].

In both the study of Raman et al [40] and McDonald et al [18] concerning the BM22 items, improvements from baseline have been reported in pain characteristics (with a mean reduction of 25.5 and 21.4 points respectively), functional interference (mean increase 23.7 and 18.8 points respectively), painful sites (mean reduction 15.8 and 13.5 points respectively) and finally in psychosocial aspects (mean increase 11.2 and 6.2 points respectively).

The results of these studies showing the changes of pain, constipation, physical functioning, appetite loss, sleep, global health scale, fatigue, emotional functioning, role functioning, dyspnea, financial issues, nausea/vomiting, cognitive functioning, social functioning from baseline to 4 weeks after treatment are demonstrated in Table 2.

II. The Brief Pain Inventory (BPI)

The authors using the BPI questionnaire to measure patients' QoL examined in our review are listed on Table 4. In their studies, all of them define radiation response according to the guidelines determined by the International Bone Metastases Consensus [36] taking into consideration analgesic consumption and pain scores. Daily opioid analgesic intake was recorded in every one of them and oral morphine equivalent dosage (OMED) was converted to milligrams per day.

All BPI functional interference items significantly improved in those 7 trials, all of which proved to be profited by RT for painful BMs one month after it was completed (Table 3).

Wu et al [32] attempted to examine pain relief and QoL after RT in patients with BMs, in a study they published in 2006. Although no differentiations were made between responding and non-responding patients, statistically significant improvements were observed in all 7 interference parameters of the BPI the first month after treatment. With the exception of social relationships, which demonstrated no statistically significant alterations, all functional interference elements appeared to benefit significantly from Worst Pain improvement (mean score change: 3.4 on the 11-point scale). Among the remaining elements, general activity marked the next biggest change (by 2.4 points), followed by mood and normal work items (changing by 2.1 points each), enjoyment of life (2 points), sleeping problems (1.9) and walking ability (improved by 1.8 points from baseline) [32].

After one month of receiving palliative irradiation, all functional interference scores in Rs included at the trials of Nguyen et al [30] and Hadi et al [31] showed meaningful improvement. Nguyen et al [30] observed significant pain relief in Rs, while Hadi et al [31] found a link between response to pain and improvement in every item's mean score apart from mood, relations with others, and sleep-

Table 4. Studies employing the BPI questionnaire

Authors, [REF] Publication time	*Enrollment period*	*Population*	*Follow-up time*
Wu et al. [32], 2006	Jul 2002- Jul 2005, Tom Baker Cancer Centre, Alberta	Pts with painful BMs referred for palliative RT N=109	Weeks 4-6 post-RT
Harris et al. [33], 2007	May 2003- Jun 2005 Toronto Sunnybrook Regional Cancer Centre	Patients with BMs referred for pain palliation to the N=101	2 Months post-RT
Hadi et al. [31], 2008	May 2003- Jan 2007 Toronto Sunnybrook Regional Cancer Centre	Patients referred for palliative RT of symptomatic BMs N=348	Weeks 4, 8 and 12 post-RT
Nguyen et al. [30], 2010	May 2003- Jun 2005	Patients with spinal metastases receiving palliative RT N=109	Months 1,2 and 3 post-RT
Zeng et al. [22], 2012	May 2003- Jun 2007	Patients referred for palliative RT of symptomatic BMs N=386	Months 1 to 6 post-RT

Table 5. Changes in items' mean score from baseline to month 1 (month 2 in the case of Harris et al. [33]) on the 11-point scale

	Wu et al. [32]	*Harris et al. [33]*	*Hadi et al. [31]*	*Nguyen et al. [30]*	*Zeng et al. [22]*
Worst pain	3.4	4	4.4	3.57	3.33
General activity	2.4	3	3.4	3.06	2.94
QoL	2	3	3.5	2.99	2.2
Normal work	2.1	2.5	3.6	2.84	3.02
Sleeping problems	1.9	2	2.9	2.33	2.78
Mood	2.1	1.5	2.8	2.71	2.31
Walking ability	1.8	2	3.2	1.78	2.55
Relationships	NS	0	1.8	2.03	1.57

ing problems. Nevertheless, all QoL items in both trials demonstrated significant improvement from baseline to one month post-RT. Worst pain score had the most significant mean regression in both trials, followed by general activity (mean changes 3.06 and 3.4 respectively), enjoyment of life (2.99 and 3.5 respectively) and normal work (subsiding by 2.84 and 3.6 points respectively), disorders affecting patients' mood (by 2.71 and 2.8 points) and sleep (by 2.33 and 2.9 respectively. Limitations in walking ability also diminished (by 1.78 and 3.2 respectively), as well as relationships with others (2.03 and 1.8 respectively).

Two months post-RT Harris et al [33] reported significant changes from baseline in interference with general activity and enjoyment of life (their mean scores regressing by 3 points in each), normal work (by 2.5 on the 11-point scale), sleep and walking ability (by 2 points each), and lastly with mood (with a 1.5-point decrease in mean score) concerning Rs. No significant regression was observed in Rs' social relationships, or in any functional interference item in NRs.

Zeng et al [22] observed a significant correlation between improvements in all functional items in response to RT, with an exception in sleep disturbances during the second and the fourth month after irradiation. One month after RT, the worst pain score subsided by 3.33 points, mean interference in normal work by 3.02, general activity by 2.94, sleep disturbances by 2.78 and trouble in walking along with temper derangement and limitations in enjoying one's life dropped by 2.55, 2.31 and 2.2 points, respectively. Social relationships marked the smallest change from baseline, with only a 1.57-point decrease [22].

In Table 5 a summary is presented of the changes in parameters mean score of worst pain, general activity, Enjoyment of life, normal work, sleeping problems, mood, walking ability, relationships from baseline to month 1 (or month 2 in the case of Harris et al) on the 11-point scale.

III. The Edmonton Symptom Assessment Scale (ESAS) and other assessment tools

A total of 8 trials used tools other than the EORTC and BPI questionnaires in order to study patients' status after RT (Table 6).

Only 3 trials in total used the ESAS, none of which juxtaposed Rs with NRs (Table 7).

Pituskin et al [42] and Fairchild et al [43] demonstrated similar decreases in pain one month after RT by 3.12 and 3.5 points respectively, followed by anxiety, which had the second greatest improvement in mean score. These authors concluded that dyspnea, nausea, and appetite loss were the only ones that did not significantly abate 4 weeks post-RT. Drowsiness, tiredness and depression also showed statistically significant improvements, by 1.84, 1.75 and 1.71, respectively, while a boost in patients' sense of well-being was observed by 1.45 points.

Nevertheless, Fairchild et al [43] observed improvements in every symptom scale in the first and the fourth week after RT. Unfortunately, they recorded the percentage of patients whose symptoms subsided, without mentioning the statistical significance in the comparison drawn to baseline. The mean score changes from baseline to a month later can be seen in Table 7.

The ESAS was applied, also, by Chow et al [44], in order to assess QoL in 518 patients in weeks 1, 2, 4, 8, and 12 after RT. Improvements in both global and index pain (by 1.7 and 4.2 points respectively), anxiety and sense of well-being (by 1 point each) and depression (by 0.6) were reported in all patients after the 4-week follow-up.

Other pain tools were employed as well by authors of articles published between 1977 and 2015 (Table 6).

In the study of Gilbert et al [48] QoL was evaluated using Karnofsky performance status (KPS), a score that demonstrates patients' functional capa-

Table 6. Authors employing tools other than the EORTC and BPI questionnaires

Authors, [Ref], Publication time	*Enrollment period*	*Population*	*Follow-up time*
Gilbert et al. [48], 1977	1970- 1973	Patients with painful BMs under palliative RT N=158	Months 3, 6, 9, 12 after RT
Gaze et al. [47], 1997	Feb 1988- May 1993	Patients with painful BMs under palliative RT N=409 (total)	Weeks 1, 3-4 and every second month after RT
Nielsen et al. [49], 1998	Jan 1989- Dec 1994	Patients with painful BMs under palliative RT N=241	Weeks 4, 8, 12 and 20 after radiation schedule was completed
Salazar et al. [50], 2001	Mar 1996- Jan 1999	Patients with painful BMs under HBI N=156	Not stated
Chow et al. [44], 2004	Jan 1999- Jan 2002	Patients with painful BMs under palliative RT N=518	Weeks 1,2,4,8 and 12 after RT
Fairchild et al. [43], 2009	Aug 2006-Dec 2006	Patients with painful BMs under palliative RT N=31	Weeks 1 and 4 after RT
Pituskin et al. [42], 2009	Jan 2007- Dec 2007	Patients with painful BMs under palliative RT N=82	One month after RT was completed
Westhoff et al. [51], 2015	1996- 1998	Patients with painful BMs under palliative RT N=956	Weeks 1-12 and Months 3-24 post- RT

Table 7. Changes from baseline weeks after treatment was completed on a 10-point scale

	Chow et al. [44]	*Fairchild et al. [43]**		*Pituskin et al. [42]*
Pain (global/index)	1.7/4.2	0.94	0.71	3.12
Anxiety	1.0	0.91	0.52	2.54
Depression	0.6	0.87	0.45	1.71
Wellbeing	1.0	0.78	0.39	1.45
Drowsiness	NS	0.81	0.425	1.84
Tiredness	NS	0.81	0.42	1.75
Appetite	NS	0.77	0.325	NS
Nausea	NS	0.93	0.325	NS
Dyspnoea	NS	0.81	0.17	NS

*expressed in proportion of patients (column 1: improved/stable, column 2: only improved)

Table 8. Changes in the pain and QoL scores one month post-RT

	Gaze et al.[47] (%)
Pain response	57.20
Analgesics consumption	25.15
Spitzer QoL	10
HADS	4.76
0 pain+0 analg	14.4

Table 9. Changes from baseline after HBI expressed as % percentage decreased, increased comparing to baseline

	Salazar et al. [50]
Mean pain response	75
Net pain relief	71
Mean analgesic drug score	68
Mean performance status	34

Table 10. Improvements in month 1 post therapy from baseline (%)

	Westhoff et al. [51]	
	Both	*Rs vs NRs*
Pain	31	25
Psychological distress	6	15
Physical symptoms distress	5	13
Activity level impairment	3	13
Value Life	2	7
Health VAS	1	6

bility. The term "good" regarding QoL was referred to patients who reported being able to cope with the majority of their needs for most of their life; those constituted Level 1. Patients experiencing difficulty in mobility and grave skeletal pain were classified as Level 2. Among 120 patients, 73% experienced a complete pain relief at the irradiated site in 3 months, 63% reported having "good" QoL post-treatment, even though this status prevalence was not mentioned before RT. A considerably pain-free status was experienced by these patients who maintained the ability to walk and did not suffer from depression provoked by the continuous use of analgesics and chemotherapy [48].

The elements of HRQoL were assessed by Gaze et al [47] using the Eastern Hospital Anxiety and Depression (HAD) Scale and Spitzer's QoL Index. The latter is a 5-item tool that examines health, everyday living, activity, outlook and support. Through these, Gaze et al [47] observed a substantial benefit in the QoL and a limitation in the incidence of anxiety in Rs concerning both fractionation regimes. Pain was again the parameter that was favored most by RT, while the Spitzer QoL parameters followed with a smaller benefit. The changes in the anxiety and depression scores, as assessed by HADS, were the smallest (Table 8).

In order to evaluate QoL and pain relief, Nielsen et al [49] applied a 5-point visual analog scale that captured global QoL, analgesic consumption and pain. A benefit in QoL post-RT was reported, without significant differences between fractionation schemes, with 7% of patients achieving an excellent well-being status.

Salazar et al [50] carried out a randomized trial in 2001, in which patients were randomly assigned to receive either 8 Gy divided in 2 fractions within the same day, 12 Gy in 4 fractions in 2 days' time, or 15 Gy in 5 fractions within a period of 5 days. An improvement in QoL was recorded in patients in the second and third groups, while a significant deterioration was observed in patients randomized in the first one. With the exception of prostate cancer patients, that seemed to be most benefited by the

third regime, all the other patients, regardless of their primary malignancy, appeared to benefit from the 12 Gy and 15 Gy schedules. Mean pain score demonstrated the greatest change from baseline after HBI (6;71/9 points), followed by mean analgesic drug score (6;12/9 points) and mean performance status (1;36/4 points) (Table 9).

A meta-analysis of the Dutch Bone Metastases published in 2015 by Westhoff et al [51] observed significant improvements in QoL of patients receiving palliative RT for painful BMs. In this large trial conducted in the Netherlands from March 1996 to September 1998, 1157 patients were randomized to receive either 24 Gy in a 6-dose fractionation schedule or 8 Gy in a single dose. Changes in scores one month after RT from baseline between Rs and NRs were compared. Mean changes in score are on display in Table 10.

The outcomes of our research are consistent with those of McDonald et al [18] confirming that an improvement in QoL is observed in the majority of patients after undergoing RT.

QoL is a term not so easy to be defined and properly evaluated; the pain and psychological distress arising from bone metastases in advanced cancer patients have disastrous effects on every aspect of a person's life. These patients are aware that they have a limited time of life ahead of them; they have undergone multiple treatments, surgical or pharmacological; they have been hospitalized and suffered from both the immediate consequences of their disease and from the adverse effects of the methods intending to cure them or prolong their survival. Their bones are painful and fragile and the patients find it difficult to move or perform their daily habits and activities without suffering; additionally, they have a hard time sleeping.

Among the domains examined by the BPI questionnaire, Worst pain was the one that benefited most. On the other hand, satisfaction and attachment patterns in cancer patients that received palliative care experienced a statistically significant amelioration post-RT. This finding complies with most of the studies employing the RTOG-EORTC QoL questionnaires, both C30 and BM22.

In particular, even though there is no absolute conformity in the conclusions among the trials applying EORTC-QLQ-C30 and C15 questionnaires since their number is limited and their populations vary, one can notice certain common points in terms of the improvement in individual QoL parameters. According to these studies' outcomes, alterations in pain scores after palliative RT prevailed over those observed in the remaining domains. Physical and emotional functioning, quality of sleep, restoration of bowel motility and appetite as well as overall health were significantly correlated with pain relief; nevertheless, a precise classification of QoL items by order of the influence patients' pain regression has on them cannot be achieved. The parameters least improving after radiation - if improved at all - were most of the time social and cognitive functioning, financial problems, diarrhea (which according to all authors never seemed to improve), dyspnoea, nausea and vomiting, fatigue and role functioning.

At this point it is important to specify that among these studies, Tolia et al [39] examined not the sole impact of RT but its palliative outcomes with the concomitant use of an agent (escitalopram) with both antidepressant and analgesic effects in a relatively high dosage. In this trial, instead of taking a dose of up to 20mg escitalopram daily, patients had been prescribed to receive 30mg escitapopram per day, concomitantly with palliative RT. Their study demonstrated a remarkable surge in patients' physical, role and cognitive performance, global health and emotional status scores as well as a significant facilitation of breathing, all of which exceeded the still considerable pain relief observed. Furthermore, even though in the study of Mendez et al [41] no statistically significant changes were found in pain palliation when using the EORTC-QLQ-C30 questionnaire, the use of QLQ-BM22 revealed ameliorations in pain score that appeared to be the most prominent compared to the rest of the parameters examined.

Trials using the QLQ-BM22 questionnaire however, provided us with a clear pattern of patients' response in terms of QoL the first months after RT. The domain that was experiencing the greatest improvement in mean score was the pain characteristics parameter, while functional interference and painful sites experienced the second and third greatest regression, respectively. Psychosocial aspects (PsA) marked the least significant progress in 2 trials [27,41] with the exception of the intervention group in the study of Rief et al [37], which experienced remarkable amelioration of PsA.

Furthermore, the ESAS along with the other tools used by authors indicated that pain and anxiety according to the ESAS is the most affected by palliative RT interfering factor in HRQol of patients with uncomplicated BMs, while physical performance, overall sense of well-being and satisfaction, along with several symptom scales are also significantly improved. Social interaction still has the lowest improvement rates.

First of all, palliative RT and pain regression proved to be rarely beneficial for psychosocial/social function items. This is most probably due to the fact that these parameters are significantly

more influenced by other factors such as the constant threat of impending death, the idea of losing their loved ones or being dependent on others and less by pain and loss of mobility. Perhaps pharmaceutical treatment, exercise, group therapy and supportive programs for both patients and their family could help improve these persons' emotional state and social interaction.

A conclusion that could be drawn due to the discrepancy between the most used EORTC questionnaires is that the QLQ-BM22 questionnaire might be able to provide more accurate information on data concerning the QoL of these patients. QLQ-C30 and C15PAL are not specifically designed for these patients and they reflect general aspects of HRQoL that are influenced by an immense variety of diseases. The domains examined by these instruments, such as financial problems, diarrhea, dyspnea, cognitive impairment, nausea and vomiting might not affect patients with painful bone metastases and brief periods between follow-ups. As literature indicates so far, the separate functional and symptom scales of these two assessment tools rarely overlap [53].

Among the studies we included in our literature review, randomized control trials were relatively few, while most of them did not primarily focus on QoL improvement; overall in the existing literature, randomized control trials mainly aim to determine which is the optimal RT technique and dose fractionation scheme in order to be achieved at the same time maximal pain response, with minimal toxicity and highest survival rates [54-57]. Therefore, an effort should be made so that future randomized controlled trials focus more on the improvement or at least preservation of patients' QoL- a cardinal purpose of palliative medicine.

Limiting factors

The trials we examined- and, consequently, our reviews as well- had the disadvantage of the continuously reducing patient population since in every study, follow-up questioning after the completion of treatment was mandatory. Such a fact is expected in every study with a sample comprised of advanced cancer patients. A large number of patients were deceased or had such a deteriorated health status that made it impossible for them to be contacted or fill-in their follow-up data. As a result, patients' improvement in QoL might be overestimated in the researches' outcomes.

Another point that should be taken into account when interpreting our article's results is that trials assessing the effects of RT on patients with complicated BMs were excluded, while most of the studies we examined did not include patients re-irradiated in the past.

Another important limiting factor is that patients under- or having gone through- other kinds of treatment (e.g. chemotherapy) were sometimes included in the aforementioned studies. Adverse effects of such therapies can have tremendous effects on QoL. Thus, the aforementioned QoL improvements might be severely affected by these concomitant methods of treatment.

Ultimately, the times of follow-up varied among the trials that we examined in this article; the ideal follow-up interval is yet to be determined. In the future, researchers should try to conclude the optimal follow-up period of time, so that the aims of researchers could be achieved without patients becoming encumbered.

As one can already see, arranging the QoL domains in patients with painful BMs, based on the influence that palliative RT has on them, is quite a difficult task; perhaps even impossible. Even though so far literature is not that extended, it appears that patients with symptomatic, uncomplicated BMs responding to palliative irradiation experience a significant benefit in their QoL, with the latter ameliorating or at least not deteriorating. Pain relief in these patients after palliative RT can reach a percentage of 70%. In addition to the so far acquired knowledge, this treatment method can both achieve symptom regression and defend this subgroups' right to live their last days of life with decency.

In the years to come, researchers should use the specialized tools more frequently when carrying out trials in this patient population- such as the EORTC QLQ-BM22. They should also pay more attention to the alterations in QoL as a response to palliative treatments. Future studies should also look for the effect of other methods concomitantly recruited –such us pharmacological agents, invasive techniques, homeopathic cures, psychological consultation or exercise programs. Social interaction, frequent psychological distress and sense of well-being parameters did not improve after treatment as often and to the extent other functional scales and symptoms did; this could be attributed to the fact that these domains are influenced by a multitude of factors related to these patients' disease. Therefore, patients suffering from painful BMs should also look for other means to help them cope with the challenges they face in an emotional and social level.

Conflict of interests

The authors declare no conflict of interests.

References

1. Piccioli A, Maccauro G, Spinelli M-S, Biagini R, Rossi B. Bone metastases of unknown origin: epidemiology and principles of management". J Orthopaed Traumatol 2015;16:81-6.
2. Cai B, Nickman NA, Gaffney DK. The cost-effectiveness of external beam radiation therapy in bone metastases. Curr Opin Support Palliat Care 2013;7:278-83.
3. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25:1423-36.
4. Jones JA, Lutz ST, Chow E, Johnstone PA. Palliative radiotherapy at the end of life: A critical review. CA: Cancer J Clin 2014;64:295-310.
5. Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. Support Care Cancer 2008;16:879-89.
6. Marras F, Leali PT. The role of drugs in bone pain. Clinical Cases in Min Bone Metabol. 2016;13:93-6.
7. Smith HS, Mohsin I. Painful Boney Metastases. Korean J Pain 2013; 26:223-41.
8. Nagakura H. Palliative Radiotherapy for Bone Metastases. GanTo Kagaku Ryoho 2015;42:1346-9.
9. Coluzzi F, Mandatori I, Mattia C. Emerging therapies in metastatic bone pain. Expert Opin Emerging Drugs 2011;16:441-58.
10. Callstrom MR, Dupuy DE, Solomon SB et al. Percutaneous image-guided cryo-ablation of painful metastases involving bone: A Multicentre Trial. Cancer 2013;119:1033-41.
11. Botsa E, Mylona S, Koutsogiannis I, Koundouraki A, Thanos L. CT image-guided thermal ablation techniques for palliation of painful bone metastases. Ann Palliat Med 2014;3:47-53.
12. Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol 2017;7:4-12.
13. Chow E, Van der Linden YM, Roos D et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol 2014;15:164-71.
14. Dennis K, Makhani L, Zeng L, Lam H, Chow E. Single fraction conventional external beam radiation therapy for bone metastases: a systematic review of randomised controlled trials. Radiother Oncol 2013;106:5-14.
15. Kougioumtzopoulou A, Zygogianni A, Liakouli Z, Kypraiou E, Kouloulias V. The role of radiotherapy in bone metastases: A critical review of current literature. Eur J Cancer Care 2017;26 (6). Doi: 10.1111/ecc.12724.
16. Chow R, Hoskin P, Chan S et al. Efficacy of multiple fraction conventional radiation therapy for painful uncomplicated bone metastases: A systematic review. Radiother Oncol 2017;122:323-31.
17. Tiwana MS, Barnes M, Kiraly A, Olson RA. Utilization of palliative radiotherapy for bone metastases near the end of life in a population-based cohort. BMC Palliat Care 2016;15:2.
18. McDonald R, Ding K, Brundage M et al. Effect of Radiotherapy on Painful Bone Metastases: A Secondary Analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23. JAMA Oncol 2017;3:953-9.
19. Van der Velden JM, Verkooijen HM, Seravalli E et al. Comparing conventional radiotherapy with stereotactic body radiotherapy in patients with spinal metastases: study protocol for an randomized controlled trial following the cohort multiple randomized controlled trial design. BMC Cancer 2016;16:909.
20. Caissie A, Zeng L, Nguyen J et al. Assessment of health-related quality of life with the European Organization for Research and Treatment of Cancer QLQ-C15-PAL after palliative radiotherapy of bone metastases. Clin Oncol 2012;24:125-33.
21. Kerba M, Wu JSY, Duan Q, Hagen NA, Bennett MI. Neuropathic Pain Features in Patients With Bone Metastases Referred for Palliative Radiotherapy. J Clin Oncol 2010;28:4892-7.
22. Zeng L, Chow E, Zhang L et al. Comparison of pain response and functional interference outcomes between spinal and non-spinal bone metastases treated with palliative radiotherapy. Support Care Cancer 2012;20:633-9.
23. Fairchild A. Palliative radiotherapy for bone metastases from lung cancer: Evidence-based medicine? World J Clin Oncol 2014;5:845-57.
24. McDonald R, Chow E, Rowbottom L et al. Quality of life after palliative radiotherapy in bone metastases: A literature review. J Bone Oncol 2015;4:24-31.
25. Roos DE. Radiotherapy for neuropathic pain due to bone metastases. Ann Palliat Med 2015;4:220-4.
26. Mantyh P. Bone cancer pain: causes, consequences, and therapeutic opportunities. Pain 2013;154:54-62.
27. Zeng L, Chow E, Bedard G et al. Quality of life after palliative radiation therapy for patients with painful bone metastases: results of an international study validating the EORTC QLQ-BM22. Int J Radiat Oncol Biol Phys 2012;84:337-42.
28. Mendez LC, Padilha JL, Lima KM et al. EP-1400:Quality of Life in Responders after Palliative Radiation Therapy for Painful Bone Metastases. Radiother Oncol 2017;123:748.
29. Rief H, Bischof M, Bruckner T et al. The stability of osseous metastases of the spine in lung cancer-a retrospective analysis of 338 cases. Radiat Oncol 2013;13;8:200.
30. Nguyen J, Chow E, Zeng L et al. Palliative response and functional interference outcomes using the Brief Pain Inventory for spinal bony metastases treated with conventional radiotherapy. Clin Oncol 2011;23:485-91.
31. Hadi S, Fan G, Hird AE, Kirou-Mauro A, Filipczak LA, Chow E. Symptom clusters in patients with cancer with metastatic bone pain. J Palliat Med 2008;11:591-600.
32. Wu JS, Monk G, Clark T, Robinson J, Eigl BJ, Hagen N. Palliative radiotherapy improves pain and reduces functional interference in patients with painful bone metastases: a quality assurance study. Clin Oncol 2006;18:539-44.
33. Harris K, Li K, Flynn C, Chow E. Worst, average or cur-

rent pain in the Brief Pain Inventory: which should be used to calculate the response to palliative radiotherapy in patients with bone metastases? Clin Oncol 2007;19:523-7.

34. Miszczyk L, Tukiendorf A, Gaborek A, Wydmanski J. An evaluation of half-body irradiation in the treatment of widespread, painful metastatic bone disease. Tumori 2008;94:813-21.
35. Lee J, Hodgson D, Chow E et al. A phase II trial of palliative radiotherapy for metastatic renal cell carcinoma. Cancer 2005;104:1894-1900.
36. Lam K, Chow E, Zhang L et al. Determinants of quality of life in advanced cancer patients with bone metastases undergoing palliative radiation treatment. Support Care Cancer 2013;21:3021-30.
37. Rief H, Akbar M, Keller M et al. Quality of life and fatigue of patients with spinal bone metastases under combined treatment with resistance training and radiation therapy-a randomized pilot trial. Radiat Oncol 2014;9:151.
38. Arias F, Arrarás J, Asín G et al. To What Extent Does Radiotherapy Improve the Quality of Life of Patients With Bone Metastasis? A Prospective, Single-Institutional Study. Am J Clin Oncol 2018;41:163-6.
39. Tolia M, Fotineas A, Nikolaou K et al. Radiotherapy combined with daily escitalopram in patients with painful bone metastasis: clinical evaluation and quality of life measurements. JBUON 2014;19:819-25.
40. Raman S, Ding K, Chow E et al. Minimal clinically important differences in the EORTC QLQ-BM22 and EORTC QLQ-C15-PAL modules in patients with bone metastases undergoing palliative radiotherapy. Qual Life Res 2016;25:2535-41.
41. Mendez LC, Raman S, Wan BA et al. Quality of life in responders after palliative radiation therapy for painful bone metastases using EORTC QLQ-C30 and EORTC QLQ-BM22: results of a Brazilian cohort. Ann Palliat Med 2017;6:65-70.
42. Pituskin E, Fairchild A, Dutka J et al. Multidisciplinary team contributions within a dedicated outpatient palliative radiotherapy clinic: a prospective descriptive study. Int J Radiat Oncol Biol Phys 2010;78:527-32.
43. Fairchild A, Pituskin E, Rose B et al. The rapid access palliative radiotherapy program: blueprint for initiation of a one-stop multidisciplinary bone metastases clinic. Support Care Cancer 2009;17:163-70.
44. Chow E, Hruby G, Davis L et al. Quality of life after local external beam radiation therapy for symptomatic bone metastases: a prospective evaluation. Support Cancer Ther 2004;1:179-84.
45. Watanabe SM, Nekolaichuk CL, Beaumont C. The Edmonton Symptom Assessment System, a proposed tool for distress screening in cancer patients: development and refinement. Psychooncology 2012;21:977-85.
46. Chow E, Nguyen J, Zhang L et al. European Organization for Research Treatment of Cancer Quality of Life Group. 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 2012;118:1457-65.
47. Gaze MN, Kelly CG, Kerr GR et al. Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. Radiother Oncol 1997;45:109-16.
48. Gilbert HA, Kagan AR, Nussbaum H et al. Evaluation of radiation therapy for bone metastases: pain relief and quality of life. AJR Am J Roentgenol 1977;129:1095-6.
49. Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. Radiother Oncol 1998;47:233-40.
50. Salazar OM, Sandhu T, da Motta NW et al. Fractionated half-body irradiation (HBI) for the rapid palliation of widespread, symptomatic, metastatic bone disease: a randomized Phase III trial of the International Atomic Energy Agency (IAEA). Int J Radiat Oncol Biol Phys 2001;50:765-75.
51. Westhoff PG, de Graeff A, Monninkhof EM et al. Quality of Life in Relation to Pain Response to Radiation Therapy for Painful Bone Metastases. Int J Radiat Oncol Biol Phys 2015;93:694-701.
52. Chow E, Hoskin P, Mitera G et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Int J Radiat Oncol Biol Phys 2012;82:1730-7.
53. Zeng L, Chow E, Zhang L et al. An international prospective study establishing minimal clinically important differences in the EORTC QLQ-BM22 and QLQ-C30 in cancer patients with bone metastases. Support Care Cancer 2012;20:3307-13.
54. Gkialas I, Iordanidou L, Galanakis I, Giannopoulos S. The use of radioisotopes for palliation of metastatic bone pain. JBUON 2008;13:177-83.
55. Niang U, Kamer S, Ozsaran Z, Haydaroglu A, Kilciksiz S. The management of painful bone metastases with biphosphonates and palliative radiotherapy: a retrospective evaluation of 372 cases. JBUON 2009;14:245-9.
56. Romanos O, Solomou E, Georgiadis P, Kardamakis D, Siablis D. Magnetic resonance imaging and image analysis of post-radiation changes of bone marrow in patients with skeletal metastases. JBUON 2013;18:788-94.
57. Carvajal C, Navarro-Martin A, Cacicedo J, Ramos R, Guedea F. Stereotactic body radiotherapy for colorectal lung oligometastases: preliminary single-institution results. JBUON 2015;20:158-65.