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Review Article

Quality of life after palliative radiotherapy in bone metastases: A literature review



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ABSTRACT

Objective: To investigate the quality of life (QOL) following palliative radiotherapy for painful bone metastases.**Methods:** A literature search was conducted in OvidSP Medline (1946–Jan Week 4 2014), Embase (1947–Week 5 2014), and the Cochrane Central Register of Controlled Trials (Dec 2013) databases. The search was limited to English. Subject headings and keywords included ‘palliative radiation’, ‘cancer palliative therapy’, ‘bone metastases’, ‘quality of life’, and ‘pain’. All studies (prospective or retrospective) reporting change in QOL before and after palliative radiotherapy for painful bone metastases were included.**Results:** Eighteen articles were selected from a total of 1730. The most commonly used tool to evaluate QOL was the Brief Pain Inventory. Seventeen studies collected data prospectively. An improvement in symptoms and functional interference scores following radiotherapy was observed in all studies. The difference in changes in QOL between responders and non responders was inconsistently reported.**Conclusion:** QOL improves in patients who respond to palliative radiotherapy for painful bone metastases.© 2014 The Authors. Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

1. Introduction

Bone is one of the most common sites of metastasis in advanced cancer, present in approximately 50–75% of patients [1]. Bone metastases are especially prevalent in patients with prostate, breast, or lung primaries [2–4] and are of great concern to both physicians and patients as they can result in complications such as pathologic fractures, hypercalcemia, and spinal cord compression [2,5–7]. One of the most common symptoms of bone metastases is pain, occurring in an estimated 70% of patients [8]. Often, patients initially present with multiple bone metastases and often, multiple sites of pain. Pain may be localized or diffuse, and may worsen upon weight bearing [9]. As a consequence of bone pain, patients often have increased difficulty with activities of daily living and decreased quality of life (QOL) [8].

Radiation therapy (RT) is considered to be the standard treatment for cancer patients with symptomatic bone metastases [3,7,10,11]. Various studies have shown that approximately

60–70% of patients experience at least some degree of pain relief following RT, regardless of radiotherapy regime [5,7]. Moreover, about 25% of patients experience complete pain relief, otherwise known as a complete response [2,7]. Although pain relief is a proven benefit of radiation therapy, this is not necessarily indicative of improved QOL.

QOL is a multidimensional model that attempts to capture the physical, social, and psychological well-being of the patient [12]. Many components influence QOL, including physical symptoms of the disease, side effects of treatment, social and family support. Treatment in the advanced cancer population is palliative rather than curative in intent, meaning that the goal is managing symptoms as opposed to prolonging life [7,13]. With this goal in mind, it is important for health care providers to consider treatment in terms of not only managing symptoms, but also stabilizing or improving other factors that affect QOL.

As QOL is a subjective concept, it can be difficult to capture in an accurate and meaningful fashion [12]. Currently, various tools are employed to assess pain and QOL in advanced cancer patients and in those specifically with bone metastases. The European Organisation for Research and Treatment of Cancer (EORTC) has developed one of the most commonly used measurements for this purpose: the QLQ-C30 [13]. Associated with this measurement is

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the QLQ-C15-PAL, a reduced version of the parent QLQ-C30 designed to capture QOL outcomes in a brief internationally recognized and validated tool. The EORTC QLQ-BM22 is a sub-module of the QLQ-C30 and is an internationally recognized and validated scale used to measure QOL in bone metastases patients [7,12].

Another widely used tool is the Brief Pain Inventory (BPI), developed by Cleeland and Ryan. The BPI is a questionnaire used to determine overall pain intensity and functional interference as a result of pain. Specifically, it examines functional interference in terms of general activity, normal work, walking ability, mood, sleep, relations with others, and enjoyment of life [6]. In addition, it captures three aspects of pain: worst, average, and current intensity.

Finally, the Edmonton Symptom Assessment System (ESAS) examines symptoms on a scale of 0, representing 'absence of symptom' to 10, representing 'worst possible symptom' [14]. Symptoms captured in this questionnaire are pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, feeling of well-being, and shortness of breath. In general, symptoms given a rating of 1–3 are considered mild, 4–7 are considered moderate, and 8–10 are considered severe [14].

The objective of this review was to investigate changes in QOL following RT for painful bone metastases. Specifically, we wanted to determine whether or not those who experienced pain relief post-treatment also experienced a positive response in QOL compared to non responders.

2. Methods

A literature search was conducted using OvidSP Medline (1946–Week 4 2014), Embase (1947–Week 5 2014), and the Cochrane Central Register of Controlled Trials (Dec 2013) databases. The search was limited to English. Subject headings and keywords utilized for the search included 'palliative radiation', 'cancer palliative therapy', 'bone metastases', 'quality of life', and 'pain'.

Any publication which reported change in QOL using a validated scale following RT was included in this review. Exclusion criteria were literature reviews and articles that discussed QOL solely before radiation treatment, as well as those which only discussed pain. Titles and abstracts of articles generated in the initial search were independently screened by RM and GB and potential articles were identified. Articles were then retrieved and examined further for relevancy.

3. Results

The literature search resulted in a total of 1730 articles. Eighteen of these articles, published between 1977 and 2013, met the eligibility criteria [1,3,4,7,8,11–22]. All studies collected data prospectively, except for that by Gilbert et al. [20] who determined QOL through chart review. Only 3 of the studies were randomized control trials [3,21,22], while the rest employed no other intervention than the questionnaire.

The most commonly used tool was the BPI, used in a total of six papers [1,4,10,11,15,16]. The next most commonly used assessment tools were EORTC measures and the ESAS, which were employed in five [7,12,13,18,19] and three [8,14,17] studies, respectively. Other assessment tools included the Patient-Generated Subjective Global Assessment, net pain relief, the McGill–Melzack Score, the Spitzer scale, and others [3,20–22]. In total, eight articles [1,4,7,10,12,15,16,18] directly compared QOL in responders and non-responders, as defined by the International

Bone Metastases Consensus guidelines, while the remaining ten [3,8,11,13,14,17,19–22] made no differentiation between the two patient groups.

3.1. Brief Pain Inventory

All of the six articles that utilized the BPI reported at least some improvement in functional interference at one month following radiotherapy for painful bone metastases (Table 1). However, the specific functional items, the degree to which they improved, and whether the improvement was observed in only responders were inconsistently reported among the publications.

Wu et al. [11] published their study in 2006, which investigated pain relief and QOL following RT for patients with bone metastases. These authors reported that there was an improvement in all seven functional items of the BPI one month following treatment; however they did not differentiate between responders and non responders [11]. Nguyen et al. [1] and Hadi et al. [4] also observed an improvement in all functional interference scores post-treatment. It was reported by Nguyen et al. [1] that only mood was significantly related to responders, whereas Hadi et al. [4] concluded that all items except mood, relations with others, and sleep, were significantly related to pain response. Harris et al. [15] found a significant reduction in interference with general activity, normal work, enjoyment of life, and average functional interference in responders. No significant reduction was found for any functional interference scores in patients classified as non responders.

Zeng et al. [10] observed that improvement in all functional interference scores was significantly related to responders, except for sleeping problems at month two and four post treatment. In contrast, Khan et al. [16] reported an improvement in sleep at two and three months post RT in responders. In non responders, sleep was reported to have improved at month one and two, but then worsened at month three.

3.2. Edmonton Symptom Assessment Scale

The ESAS was used in three of the 17 included studies, none of which differentiated between responders and non responders. Both Pituskin et al. [8] and Fairchild et al. [14] concluded similar pain response post-treatment, with pain scores decreasing from 6.1/10 and 6.08/10 at baseline, to 2.6/10 and 2.96/10 post-treatment, respectively. In terms of symptoms, Pituskin et al. [8] reported that shortness of breath, nausea, and appetite were the only symptoms that did not show significant improvement at a four week follow-up. Contrastingly, Fairchild et al. [14] found improvement in all symptom severities at weeks one and four post treatment, although improvement was reported as the percentage of patients who experienced symptom relief, with no mention of the statistical significance when compared to baseline.

Chow et al. [17] also utilized the ESAS with a large population of 518 patients. These authors assessed pain and QOL at 1, 2, 4, 8, and 12 weeks post RT and observed an improvement in global pain, index pain, anxiety, and sense of well-being for all patients throughout the follow-up. All articles that employed the ESAS to measure QOL can be found in Table 2.

3.3. European Organization for Research and Treatment of Cancer quality of life questionnaires

A total of five studies used EORTC developed questionnaires; three used the QLQ-C30, one used the QLQ-C15-PAL, and one used both the QLQ-BM22 as well as the QLQ-C30 (Table 3). Miszczyk et al. [13] used the QLQ-C30 when evaluating patients who were treated with half-body irradiation for symptomatic bone

Table 1
A summary of articles using the Brief Pain Inventory (BPI) to assess QOL.

Article authors (year)	Population and time of accrual	Questionnaire administration	Responders	Non-responders	Ref
Wu et al. (2006)	July 2002–July 2005 All patients treated with palliative radiation for bone metastases N=109	Baseline and 4–6 weeks post treatment	Overall pain response of 72% Significant reduction for all 7 functional interference items after treatment with greatest improvement seen in general activity	NA	[11]
Harris et al. (2007)	May 2003–June 2005 All patients treated with palliative radiation for bone metastases N=199	Baseline and 2 months post treatment	Significant decrease in functional interference scores in general activity, normal work, enjoyment of life, and average functional interference Overall response in 66%, 58%, and 54% for worst, average, and current pain scores, respectively	No significant difference in functional interference scores Pain progression in 11%, 14%, and 13% (worst, average, current pain scores) No change in pain for 23%, 28%, and 31% (worst, average, current pain scores)	[15]
Hadi et al. (2008)	May 2003–Jan 2007 All patients treated with palliative radiation for bone metastases N=348	Baseline and Months 1, 2, and 3 post treatment	All symptom severities improved over time All symptoms except for mood, relations with others, and sleep were related to responders Response rates of 56.5%, 57.5%, and 66.7% at weeks 4, 8, and 12 respectively	NA	[4]
Nguyen et al. (2011)	May 2003–June 2005 All patients treated for spinal metastases N=109	Baseline and Months 1, 2, and 3 post treatment	All pain scores and functional interference scores improved over time Mood was the only significant BPI functional item significantly related to responders	All BPI scores were significantly improved following RT except for mood	[1]
Khan et al. (2011)	May 2003–June 2007 Patients treated with radiation for bone metastases N=400	Baseline and months 1, 2, and 3 post treatment	Improvement in sleep at week 4, 8, and 12	Improvement in sleep at weeks 4 and 8, worsened at week 12	[16]
Zeng et al. (2012)	May 2003–June 2007 Patients treated with radiation for bone metastases N=386	Baseline and each month for 6 months post treatment	Improvement in pain and functional interference scores significantly related to responders, regardless of spine or non-spinal location, except for sleeping problems at month 2 and 4	NA	[10]

metastases. Not only did pain decrease from 6.1 at baseline to 3.1 two weeks post-treatment, but all five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning) also demonstrated improvement over time. The same held true for global QOL, and all symptom scales except for diarrhea and financial difficulties [13].

Another study, conducted by Lee et al. [18] investigated pain relief and QOL in patients with metastatic renal cell carcinoma. Although this study did not focus solely on bone metastases in these patients, 25 of a total of 31 patients were radiated for painful bone metastases. Improvement in QOL was reported by 33% of patients, no significant change by 21%, and decline in QOL by 46%. Physical functioning was reported as improved in 48% of patients and symptom improvement in 22% of patients [18].

A study conducted by Lam et al. [19] used the QLQ-C30 and reported improvement in physical and emotional functioning, global health score, pain, insomnia, constipation, and financial problems following RT. No differentiation between responders and non responders was made [19].

The QLQ-BM22, in conjunction with the QLQ-C30, was used in a study conducted by Zeng et al. [7]. Fifty-nine patients had complete follow-up data of which 22, 8, and 29 experienced a partial response, pain progression, and an indeterminate response, respectively. Lower scores for painful sites, painful characteristics, and pain were seen at follow-up for responders when compared to non-responders. Responders also experienced improved physical and role functioning, as well as functional interference and constipation. Improvement, although not significant, was seen in psychosocial aspects and global health status in responders compared to non responders [7].

Caissie et al. [12] used the QLQ-C15-PAL in their study of 178 patients with symptomatic bone metastases. Overall radiotherapy response was seen in 45% of patients at week 1, 62% at week two and month 1, and 65% at month 2. In responders, overall QOL significantly improved two months post radiation therapy. Furthermore, improvement was also seen in emotional functioning, fatigue, insomnia, constipation, and pain. Contrastingly, no improvement was seen in overall QOL, functioning, or symptoms in non responders [12].

3.4. Other pain and quality of life assessments

A variety of other pain assessments were used in studies published between 1977 and 2001 (Table 4). Gilbert et al. [20] used Karnofsky Performance Status (KPS), which measures functional impairment, to assess QOL. Patients who spent most of their life being able to care for most of their own needs were considered

to have “good” QOL, defined as Level 1. Those with difficulty ambulating and extreme skeletal pain were categorized as Level 2. Of 120 total patients, 63% experienced “good” QOL post-treatment, although the prevalence of such was not reported before treatment [20].

Gaze et al. [3] investigated symptoms and QOL using Eastern Hospital Anxiety and Depression (HAD) scale and Spitzer's QOL Index. Spitzer's QOL Index is a five item questionnaire about activity, daily living, health, support, and outlook. Using these tools, Gaze et al. [3] reported a decreased prevalence of anxiety and depression and improved QOL in responders for both fractionation schedules.

Nielsen et al. [21] assessed pain relief and QOL through a 5 point visual analog scale that included pain, global QOL, and analgesic consumption. Similarly to Gaze et al. [3], they reported an increase in QOL regardless of fractionation schedule, with a total of 7% of patients experiencing a complete feeling of well-being.

A randomized trial was conducted by Salazar et al [22] in 2001 in which patients were randomized to receive 15 Gy in 5 fractions in 5 days, 8 Gy in 2 fractions in 1 day, or 12 Gy in 4 fractions in 2 days. The authors found an improvement in QOL in patients with the first and third radiation schedule, but significantly worse QOL in patients randomized to the second schedule. This was consistent for all primaries except prostate, in which the first protracted schedule (15 Gy in 5 fractions in 5 days) was favoured.

4. Discussion

As a multidimensional concept that encompasses the well-being of the whole person, QOL is both difficult to define and measure. Often, bone metastases cause pain which decreases mobility and interferes with physical functioning. In turn, this may lead to an inability to seek support from friends and family, causing emotional and psychological distress. In an article written by Carlson et al. [23], distress was defined as “normal feelings of vulnerability, sadness, and fears, to problems that can become disabling such as depression, anxiety, panic, social isolation, and spiritual crisis”. These authors stated that distress is associated with reduced survival and QOL, and that both pain and fatigue are highly validated components of distress. This was further confirmed in a study conducted by Kaasa et al. [24], who showed that psychological distress is related to pain and reduced performance status.

Currently, treatment response is defined by the International Bone Metastases Consensus guidelines in terms of pain score and analgesic consumption [25]. It is hypothesized that, if

Table 2

A summary of articles that employed the Edmonton Symptom Assessment Scale (ESAS) to measure QOL.

Article authors (year)	Population and time of accrual	Questionnaire administration	Responders	Non-responders	Ref
Chow et al. (2004)	Jan 1999–Jan 2002 All patients treated with palliative radiation for bone metastases N=518	Baseline, and 1, 2, 4, 8, 12 weeks post treatment	Improvements in global pain, index pain, anxiety, and sense of well-being for all patients	NA	[17]
Pituskin et al. (2009)	Jan 2007–Dec 2007 All patients treated with palliative radiation for bone metastases N=82 ^a	Baseline and 1 month	Improvement in mean follow-up pain score, all symptoms except for shortness of breath, nausea, and appetite significantly improved by 4 weeks	NA	[8]
Fairchild et al. (2009)	Aug–Dec 2006 Patients treated with palliative radiation for bone metastases N=31	Baseline and week 1 and 4 post treatment	Improvement or stabilization in nausea (93%), anxiety (91%), depression (87%), fatigue (81%), drowsiness (81%), shortness of breath (81%), well-being (78%), and appetite (77%)	NA	[14]

^a Patient-Generated Subjective Global Assessment (PG-SGA) was also utilized.

Table 3

A summary of articles using European Organization for Research and Treatment of Cancer (EORTC) measurements to assess QOL.

Article authors (year)	Population and time of accrual	Assessment tool	Questionnaire administration	Responders	Non-responders	Ref
Lee et al. (2005)	1996–2002 Patients with metastatic renal cell carcinoma, <i>N</i> =31 Patients with metastatic renal cell carcinoma being treated for symptomatic bone metastases, <i>N</i> =25	EORTC QLQ-C30 and McGill-Melzack score	Baseline, Months 1 and 3 post treatment, and every 3 months for one year post treatment	83% had a decrease in site-specific pain 33% reported increase in quality of life by 2 months Increase in physical functioning measured by EORTC QLQ-C30 in 48% of patients	No significant change in quality of life in 21% Worsening in global quality of life at 1 month by 46% of patients	[18]
Miszczuk et al. (2008)	May 2001–Sept 2006 All patients with bone metastases treated with single half-body irradiation <i>N</i> =95	EORTC QLQ-C30	Baseline, week 2, week 4, and every month post treatment until death or too ill to respond	Decrease in use of strong opioids Increase in those who do not need analgesics Significant increase in physical, role, emotional, and social functioning after treatment Improvement in global quality of life Decrease in symptoms except diarrhea and financial difficulties	NA	[13]
Caissie et al. (2012)	Oct 2007–July 2010 Patients treated with palliative radiation for bone metastases <i>N</i> =178	QLQ-C15-PAL	Baseline, week 1, week 2, month 1 and month 2 post treatment	Significant decrease in pain, insomnia, and constipation at 1 month follow-up Significant increase in quality of life by month 2 Pain score improved to 2.6/10	No significant improvement in any QLQ-C15-PAL measurement	[5]
Zeng et al. (2012)	Mar 2010–Jan 2011 Patients treated with radiation for bone metastases <i>N</i> =59	QLQ-BM22, QLQ-C30	Baseline and month 1 post treatment	By month 1 follow-up, improvement in three of four QLQ-BM22 domains (painful site, painful characteristic, functional interference) and 3 QLQ-C30 domains (physical functioning, role functioning, and pain) Decrease in constipation Psychosocial aspects and global health status improved	Patients with pain progression had worse functional interference	[7]
Lam et al. (2013)	Mar 2010–Jan 2011 Patients treated with radiation for bone metastases <i>N</i> =350	QLQ-C30	Baseline and 1 month follow-up	Improvement in physical functioning, emotional functioning, global health score, pain, insomnia, constipation, and financial stressors	NA	[19]

Table 4

A summary of articles using assessment tools other than the Brief Pain Inventory, Edmonton Symptom Assessment Scale, or European Organization for Research and Treatment of Cancer measurements.

Article authors (year)	Population and time of accrual	Assessment Tool	Questionnaire Administration	Responders	Ref
Gilbert et al. (1977)	1970–1973 Patients treated with radiation for bone metastases N=158	Level 1 – Ability to care for most personal needs Level 2 – Require major help in self-care	Baseline and once every three months for one year or until death	74% achieved local pain free at 3 months QOL considered “good” in 63%, meaning they were relatively pain free, could ambulate	[20]
Gaze et al. (1997)	Feb 1988–May 1993 Patients treated with radiation for painful bone metastases, comparing a single 10 Gy treatment or 22.5 Gy/5 N=200 and 209 for Hospital Anxiety and Depression Questionnaire and Spitzer’s Index, respectively	Hospital Anxiety and Depression, Spitzer’s QOL Index	Baseline, week 1, weeks 3–4, and every 2 months post treatment	Prevalence of anxiety and depression decreased for both schedules Quality of life improved for both schedules	[3]
Nielsen et al. (1998)	Jan 1989–Dec 1994 Patients treated with radiation therapy for painful bone metastases randomized to be treated with 8 Gy/1 or 20 Gy/4 N=241	Visual Analog Scale (VAS) and 5 point categorical pain scale, global QOL, and analgesic consumption	Baseline, and weeks 4, 8, 12, and 20 post treatment	At 4 weeks post treatment, similar improvement in VAS QOL seen in patients in both treatment arms with 20Gy/4	[21]
Salazar et al. (2001)	Mar 1996–Jan 31, 1999 Patients treated with half-body radiation for painful bone metastases, randomized to receive 15Gy in 5 fractions in 5 days, 8Gy in 2 fractions in 1 day, and 12Gy in 4 fractions in 2 days N=156	Net pain relief as designed by RTOG (divide pain free survival time by overall survival, then multiple by 100%= remaining life % spent pain free without retreatment) QOL assessed using net pain relief concept	Undefined	91% achieved some response, 45% achieved complete response Average net pain relief= 71% Improvement in initial performance status and narcotic use, and as a result, improvement in QOL for patients randomized to the first and third radiation schedules	[22]

psychological distress is related to pain and reduced performance status, an improvement in pain will lead to an improvement in psychological aspects of one's health and QOL. Our literature review confirmed that the majority of patients experience an improvement in QOL following RT; however, it is unknown which aspects of QOL improve, and the degree to which this improvement is related to pain response.

Part of the difficulty in determining which aspects of QOL improve is due to the wide range of questionnaires used. Although there has been an effort to standardize assessment tools in recent years, for example with the development of the QLQ C15-PAL and the BM22, there still remains an inconsistent approach to assessing QOL. This makes it difficult to compare the individual functional interference items and symptom scales between questionnaires. Future studies are required to determine the most valid and reliable QOL questionnaire. This questionnaire should then be employed in a large prospective study investigating the possible existence of a positive correlation between pain relief and improvement in QOL following palliative radiotherapy for painful bone metastases.

Only three of the 18 studies were randomized control trials [3,21,22], all of which were exploring the use of fractionation schedule and radiation technique. Numerous other randomized control trials have investigated similar questions; however their primary endpoints are often pain score, survival, and toxicity. It is important for the endpoints of these randomized control trials to be reconsidered to include QOL because its maintenance or improvement is such a vital goal of palliative treatment.

4.1. Limitations

In studies investigating variables in a palliative cancer population, patient attrition is always one of the main limitations. This is a limitation in all studies included in this review, as all studies involved post-radiation follow-up at which point patients could either have died or become no longer contactable. In addition, only patients who were well enough to complete follow-up questionnaires were included in follow-up data. As such, those who have a poorer QOL and physical functioning may not be able to provide data. Results may overestimate an improvement in QOL as a result.

These studies are also limited in that they do not exclude those who are on other cancer treatments, including hormone therapy and chemotherapy. These anti cancer therapies are associated with side effects which may impact QOL. Therefore, the accuracy of reported changes in QOL is confounded by these treatments.

Finally, it is noted that a variety of follow-up schedules were used across the studies included in this review. Evidently, the optimal duration of time to follow these patients is unknown. Future studies would be useful in determining an appropriate period of follow-up, in order to ensure that trial endpoints can be reached without placing too much burden on patients.

5. Conclusion

Overall, despite somewhat contradicting results and limited literature, it seems that there may be at least some improvement or stabilization in QOL in patients who respond to radiation therapy. This, combined with the knowledge that 60–70% of patients experience pain relief post-treatment, satisfies the goals of palliative treatment: to manage symptoms and improve or stabilize QOL. Future studies using a validated questionnaire that look at a correlation between responders to RT and improvement in QOL would be useful in determining the degree to which QOL can be expected to improve following treatment. This would be useful to allow informed decision making for both patients and

physicians, especially when offering treatment to patients with lower performance status and poorer prognosis.

Conflict of Interest:

The authors have no conflicts of interest to disclose.

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