



The Burden of Metastatic Cancer–Induced Bone Pain: A Narrative Review

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Abstract: Bone pain is one of the most common forms of pain reported by cancer patients with metastatic disease. We conducted a review of oncology literature to further understand the epidemiology of and treatment approaches for metastatic cancer–induced bone pain and the effect of treatment of painful bone metastases on the patient’s quality of life. Two-thirds of patients with advanced, metastatic, or terminal cancer worldwide experience pain. Cancer pain due to bone metastases is the most common form of pain in patients with advanced disease and has been shown to significantly reduce patients’ quality of life. Treatment options for cancer pain due to bone metastases include nonsteroidal anti-inflammatory drugs, palliative radiation, bisphosphonates, denosumab, and opioids. Therapies including palliative radiation and opioids have strong evidence supporting their efficacy treating cancer pain due to bone metastases; other therapies, like bisphosphonates and denosumab, do not. There is sufficient evidence that patients who experience pain relief after radiation therapy have improved quality of life; however, a substantial proportion are nonresponders. For those still requiring pain management, even with available analgesics, many patients are undertreated for cancer pain due to bone metastases, indicating an unmet need. The studies in this review were not designed to determine why cancer pain due to bone metastases was undertreated. Studies specifically addressing cancer pain due to bone metastases, rather than general cancer pain, are limited. Additional research is needed to determine patient preferences and physician attitudes regarding choice of analgesic for moderate to severe cancer pain due to bone metastases.

Keywords: cancer, pain, bone, metastasis, quality of life, cancer patients

Introduction

Bone metastases are a significant contributor to the cancer-induced pain felt by over half of patients with metastatic cancer.^{1,2} In fact, bone pain is often the initial symptom of bone metastasis.^{3,4} The pain may come and go at first, becoming constant and gradually intensifying with time.⁵ Patients often experience worsening background pain in the months leading up to a diagnosis of bone metastasis.⁶ After a bone metastasis diagnosis, the proportion of patients experiencing pain may continue to rise at a slower rate than before diagnosis, likely as a result of more intensive patient management, including the introduction or intensification of pain medications.⁶ Severe spontaneous (ie breakthrough) pain occurs frequently, with acute and unpredictable occurrence and severity.⁵ Higher pain levels correlate with greater functional impairment.⁷

Metastatic cancer–induced bone pain (mCIBP) is caused by inflammation and bone remodeling (nociceptive pain) or by damage to or dysfunction of the nervous system (neuropathic pain) due to tumor invasion.^{8,9} Increasingly, research indicates that cancer-induced bone pain is often a combination of neuropathic and nociceptive pain, rather than distinct neurochemical events.¹⁰ Pain from persistent nerve activation or damage from bone metastases may result in peripheral or central sensitization.⁹ Cancer pain due to bone metastases may be background (tonic) pain, spontaneous at rest, related

to movement (incident pain), or breakthrough pain, defined as a transitory flare of pain superimposed on an otherwise stable pattern under opioid therapy.^{7,11} These types of pain may be present alone or in combination. Incident pain can be managed by increasing the opioid dose above that which is effective for controlling pain at rest.¹¹ Breakthrough pain is often unpredictable, sudden in onset (< 5 minutes from start of pain escalation until maximum pain), of short duration (often < 15 minutes), and particularly debilitating for patients.^{7,12,13}

In this review, we describe the epidemiology of bone metastases by cancer type, the prevalence and severity of pain associated with bone metastases, the impact of this pain on health-related quality of life (HRQOL), and the effectiveness of current treatments on cancer pain due to bone metastases and on patients' HRQOL. While many patients find some pain relief through current therapeutic methods and improvement in HRQOL from radiation treatment, our findings also identify patients' unmet needs, with the hopes of providing guidance for future research.

We conducted a targeted literature review using search terms for cancer pain and epidemiology, HRQOL, practice patterns, and treatment guidelines to search literature databases (PubMed, Embase, Cochrane Library, and EconLit) for publications in the last 10 years; the search was conducted on August 20, 2020. We also searched the 2018–2020 meeting abstracts from key congresses (American Society of Clinical Oncology, European Society for Medical Oncology, European Pain Federation, International Society for Pharmacoeconomics and Outcomes Research, and National Comprehensive Care Network). We included reviews or primary studies of cancer pain due to bone metastases in adults.

Epidemiology of Cancer Pain

According to Smith et al's systematic review of 122 cancer pain studies across disease subtypes, cancer pain is a prevalent issue for cancer patients, as 66.4% of patients with advanced, metastatic, or terminal cancer experienced pain related to their cancer.¹⁴ Further analysis showed that 51.9% of all patients with advanced, metastatic, or terminal cancer experienced moderate to severe cancer pain.

Cancer pain can result from a number of causes, but bone metastases are the most common cause in advanced disease.¹⁵ Bone metastases are relatively uncommon at initial cancer diagnosis but become increasingly common as the cancer metastasizes (Table 1). For most solid tumors, the incidence rate of bone metastases at initial diagnosis is in the single digits; however, 4.1–23.0% of patients in the United States (US) and up to 20.0% of patients in Japan present with bone metastases at their initial diagnosis with lung cancer.^{16–18} Still, at the initial diagnosis of metastatic cancer, nearly 40% of patients with kidney and renal pelvis cancer, 65% of patients with breast cancer, and 89% of patients with prostate cancer present with bone metastases.^{16,17,19} Overall, nearly 70% of patients with metastatic prostate cancer or breast cancer experience bone metastases.^{20–22} Additionally, most patients who do develop bone metastases experience pain. Across all cancer subtypes, approximately 80% of patients with bone metastases report moderate to severe bone pain.²³ Routine assessment of the patient's pain intensity is critical for effective pain management. Pain intensity is categorized as mild, moderate, or severe and treated accordingly, as described below.

Impact of Cancer Pain Due to Bone Metastases on HRQOL

The reduced quality of life experienced by cancer patients at an advanced disease state, who are often also experiencing treatment side effects, are compounded by mCIBP (Table 2). Cross-sectional studies of bone metastases arising from any primary cancer found that pain from bone metastases is associated with poorer HRQOL and worse physical function.^{24,25} Among the 174 patients with bone metastases in Japan surveyed by Shinoda, et al,²⁴ the mean EQ-5D quality of life (QOL) score was found to be 0.58, lower than the population average of 0.85. Additionally, although physical function tends to worsen as patients' pain intensity increases, the correlation between these two outcomes was reported as moderate in a study of 211 patients with cancer pain due to bone metastases.²⁵ The authors could not definitively state that there was a causative relationship between pain intensity and physical function because of the presence of confounding variables (eg, tumor histology, disabling conditions). Higher bone pain severity was associated with significantly lower scores on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core (EORTC QLQ-C30) generic cancer (Table 2). Patients with severe pain had a 21-point reduction in Global Health Status (GHS) score/QOL (as measured using EORTC QLQ-C30; total

Table I Incidence Rates of Cancers by Country and Proportion with Bone Metastases

Measure and Timing of Bone Metastasis Diagnosis	Prostate	Breast	Lung	Renal	Colon or Colorectal Cancer
Age-standardized incidence of cancer per 100,000 (world) ⁹⁶ (all stages)	US: 75.7 Japan: 35.4 France: 99.0 Germany: 63.2 Italy: 61.3 Spain: 73.1 UK: 80.7	US: 84.9 Japan: 57.6 France: 99.1 Germany: 85.4 Italy: 92.8 Spain: 75.4 UK: 93.6	US: 35.1 Japan: 27.5 France: 36.1 Germany: 33.7 Italy: 24.4 Spain: 27.0 UK: 32.5	US: 10.9 Japan: 7.2 France: 12.5 Germany: 8.7 Italy: 9.0 Spain: 8.7 UK: 10.2	US: 25.6 Japan: 38.9 France: 30.4 Germany: 26.2 Italy: 29.9 Spain: 33.4 UK: 32.1
Incidence proportion: bone metastases at cancer diagnosis	US: 5.1–5.7% ^{16,97}	US: 3.6–7.1% ^{1,16,17,19}	US: 4.1–23.0% across types ^{16,17} Japan: 20.0% ¹⁸	US: 3.3–16.1% ^{16,17,98}	US: 1.20–1.24% ^{16,99} SLR: 2.9–6.6%; followed until death, 10% ¹⁰⁰
Incidence proportion: bone metastases at metastatic cancer diagnosis	US: 88.7–89.6% ^{16,17}	US: 53.7%–65.6% ^{16,17,19}	US: 18.0–39.1% across types ^{16,17} Reviews: 30–40% ²¹	US: 39.6% ¹⁷	US: 5.9% ¹⁶
Prevalence proportion in metastatic patients	US: 71%; mCRPC: 100% ²⁰ Reviews: 65%–75% ^{21,22}	NR	NR	20–25% ²¹	NR

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; NR, not reported; SLR, systematic literature review; UK, United Kingdom; US, United States.

possible score = 100) compared with those who had no bone pain or only mild/moderate bone pain ($P < 0.05$) and an 18-point reduction in their physical functioning score compared with those with mild or no bone pain ($P < 0.05$).

Treatment Strategies and Outcomes

Several organizations have issued treatment guidelines for cancer pain, some of which are specifically for mCIBP.^{26–28} Other guidelines for cancer pain have sections on the treatment of bone metastases and related pain.^{8,29} In a European Society for Medical Oncology (ESMO) guideline subsection specifically on bone pain, Fallon et al⁸ state that external beam radiation therapy (EBRT) is the first line of treatment for cancer pain due to bone metastases, preceding or concurrent with analgesics if pain from uncomplicated bone metastases continues.⁸ Guidelines issued by the World Health Organization, ESMO, and the Spanish Society for Medical Oncology for the treatment of CIBP or mCIBP advocate a stepwise approach for pharmacological and minimally invasive therapies, using the mildest agents first (nonsteroidal anti-inflammatory drugs [NSAIDs] ± adjuvants), and if pain relief is inadequate, adding opioids, then minimally invasive procedures.^{8,30,31} Pain control should be evaluated to maintain medication at the lowest required doses.^{31,32}

Radiation Therapy

Pain relief is obtained in 60% to 80% of patients with mCIBP treated with EBRT, including complete pain relief for 30%.⁸ Stereotactic body radiotherapy administers very high ablative doses of concentrated radiation but avoids radiation damage to critical normal tissues.⁸ Several representative studies have shown that patients who respond to palliative radiation therapy (RT) for painful bone metastases also experience improvements in functional outcomes and HRQOL (Table 3).^{33–38} These effects appear to be independent of the treatment regimen, which varies from a single dose of 8 grays (Gy) to longer treatment regimens (30 Gy in 10 fractions).^{34,35,39,40} Although a single 8-Gy fraction is equally effective for pain relief and is more cost-effective than higher fractionated doses of RT,^{41,42} it is associated with a higher incidence of retreatment.⁴¹

In a prospective study involving 75 patients with painful bone metastases from prostate cancer treated with palliative RT, 81% experienced at least some form of pain relief, with 23% of patients experiencing complete relief following

Table 2 Effect of Cancer Pain Due to Bone Metastasis on HRQOL

Reference, Country	Design/ Population	Patient-Reported Outcomes, Statistically Significant Results
Shinoda et al (2019) ²⁴ Japan	<ul style="list-style-type: none"> • Cross-sectional survey of patients (N = 174) with bone metastases from any kind of cancer (top 2: lung and breast) in university hospital setting • Mean age, 64.7 years • SREs: N = 174; RT, 43.1%; fracture, 17.8%; paralysis, 13.2%; surgery, 4.2% 	<p>Patients with higher pain scores (7–10 vs 0–6) had worse QOL as assessed via:</p> <ul style="list-style-type: none"> • EQ-5D**** • EORTC QLQ-C15-PAL**** <ul style="list-style-type: none"> – GHS/QOL scale, physical functioning, emotional functioning scales, and all symptoms except nausea and vomiting • EORTC QLQ- BM22*** <ul style="list-style-type: none"> – painful sites****, pain characteristics****, and functional interference**** – psychosocial aspects** • K6 distress scale***
Janssen et al (2019) ²⁵ Netherlands	<ul style="list-style-type: none"> • Cross-sectional survey of patients (N = 211) with bone metastases from any kind of cancer • Mean age, 63 years • Previous surgery for bone metastasis, 56% • Previous RT for bone metastasis, 54% 	<ul style="list-style-type: none"> • Better functioning as measured by PROMIS Physical Function Cancer questionnaire was associated with: <ul style="list-style-type: none"> ○ Having prostate*** and thyroid carcinoma** (vs breast carcinoma) ○ Not having other disabling conditions* • Less pain as measured by PROMIS Pain Intensity questionnaire was associated with: <ul style="list-style-type: none"> ○ Having lymphoma** or prostate cancer** (vs breast carcinoma) • A moderate correlation was observed between pain and physical function***, suggesting that patients with more intense pain have worse physical function

Note: **** $P < 0.0001$; *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$.

Abbreviations: EQ-5D, 5-dimension EuroQoL questionnaire; EORTC QLQ-BM22, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Bone Metastases module; GHS, Global Health Status; K6 distress scale, Kessler Psychological Distress Scale 6; PROMIS, Patient-Reported Outcomes Measurement Information System; EORTC QLQ-C15-PAL, EORTC Quality of Life Questionnaire–Core 15 Palliative; QOL, quality of life; RT, radiation therapy; SRE, skeletal-related event.

treatment.³⁶ Significant improvements in physical functioning, social functioning, and global QOL scales of the EORTC QLQ-C30 persisted for at least 3 months, disappearing at 6 months' posttreatment. Reduction in pain, fatigue, dyspnea, and sleep disturbance was also seen at 1 month and at 3 months but reoccurred at 6 months.

Similar results were observed in a separate study in which HRQOL was assessed using the EORTC Quality of Life Questionnaire Core-15 Palliative (EORTC QLQ-C15-PAL).³⁸ Patients (n = 178) scheduled to receive palliative RT for painful bone metastases were assessed at Week 1, Week 2, Month 1, and Month 2 after receiving RT. Response to RT was defined according to the International Bone Metastases Consensus criteria⁴³ as complete response (CR), partial response (PR), stable pain, or pain progression. Among those patients, 45% experienced either CR or PR at Week 1, which increased to 62% of patients at Week 2 and 65% at Month 2. Significant reductions in pain, insomnia, and constipation were seen by Month 1, and overall QOL improved significantly by Month 2 for patients who responded to RT. The proportion of nonresponders (patients with stable pain or pain progression) decreased over time from 54% at Week 1 to 38% at Week 2 and 35% at Month 2. Nonresponders had no improvement in median scores for overall QOL or functioning scales.

The EORTC QLQ-Bone Metastases module (EORTC QLQ-BM22) was used to assess bone metastasis-specific HRQOL in a multinational study involving 59 patients undergoing palliative RT.⁴⁴ One month after RT, patients who responded to RT significantly improved in three of four QLQ-BM22 domains (painful site, painful characteristic, and functional interference) and three QLQ-C30 domains (physical functioning, role functioning, and pain). Patients with pain progression had significantly worse functional interference and pain compared with those who had a PR.

Studies specifically examining the benefits of palliative RT on spinal metastases showed pain scores decreased significantly after RT. A comparison between the outcomes for patients with spinal metastases versus nonspinal

Table 3 Effect of Radiation Therapy on Cancer Pain Due to Bone Metastases

Reference, Country	Design/Population	Patient-Reported Outcomes, Statistically Significant
EBRT or RT Di Lorenzo et al (2003) ³⁶ Italy	<ul style="list-style-type: none"> • Prospective clinical study of patients (N = 75) with bone metastases from prostate cancer who relapsed after first-line hormonal therapy and received palliative RT (EBRT) • Median age, 68 years • Patients were also receiving: second-line hormonal therapy, 27%; chemotherapy, 33%; and bisphosphonates, 60% • 40% received EBRT alone • Bone sites to be irradiated: pelvis, n = 59; vertebral column, n = 34; long bones, n = 12; ribs/externa, n = 5 	<ul style="list-style-type: none"> • EORTC QLQ-C30 questionnaire 1 month after RT treatment; significant improvements for at least 3 months in the following: <ul style="list-style-type: none"> – Physical functioning, <i>P</i> = not reported – Social functioning, <i>P</i> = not reported – Global quality of life, <i>P</i> = not reported
Caissie et al (2012) ³⁸ Canada	<ul style="list-style-type: none"> • Prospective clinical study of patients (N = 178) scheduled to receive palliative RT for CaPBM from any cancer^a • Median age, 69 years • Systemic anticancer therapy within 1 week of RT consultation: <ul style="list-style-type: none"> – No, 64% – Yes, 36% • RT treatment sites: thoracic/lumbar spine, n = 64; leg/hip, n = 48; pelvis/sacrum, n = 38; arm/shoulder, n = 14; chest/rib, n = 11; others, n = 3 	<ul style="list-style-type: none"> • EORTC QLQ-C15-PAL, significant decreases in symptoms by 1 and/or 2 months in all patients: <ul style="list-style-type: none"> – Pain by both 1**** and 2**** months – Insomnia by 1 month**** – Constipation by 1 month** • EORTC QLQ-C15-PAL, significant improvements by 1 and/or 2 months after RT in RT responders: <ul style="list-style-type: none"> – 1 month – Insomnia*** – Dyspnea* – Both 1 and 2 months – Emotional functioning at 1** and 2 months** – Pain at both 1**** and 2 months**** – Constipation at 1** and 2* months – 2 months – Overall QOL**
Zeng et al (2012) ⁴⁴ Canada (44%), Cyprus, Egypt, Brazil, India, and France	<ul style="list-style-type: none"> • International trial validating the EORTC QLQ-BM22 in patients (N = 79) with bone metastases from any cancer^a who underwent RT • Median age, 65 years • Radiation sites: NR 	<p>n = 59 with complete QOL follow-up data</p> <p>At 1 month after RT, significant differences among patients with partial responses, indeterminate responses, or pain progression:</p> <ul style="list-style-type: none"> • QLQ-BM22 scale <ul style="list-style-type: none"> – Painful site**** – Painful characteristic**** – Functional interference**** • QLQ-C30 scale <ul style="list-style-type: none"> – Physical functioning*** – Role functioning** – Pain****
Zeng et al (2012) ⁴⁵ Canada	<ul style="list-style-type: none"> • Prospective study in patients (N = 386) receiving palliative RT for bone metastases from any cancer^a <ul style="list-style-type: none"> – n = 129 receiving RT to the spine – n = 257 receiving RT to nonspinal bones • Median age, 68 years • Current pain at initial RT consultation using BPI <ul style="list-style-type: none"> – Mean (SD), 3.71 (2.75) – Median (range), 3.0 (0-10) 	<p>None: There were no statistically significant differences from baseline in mean BPI^b functional interference items' scores at 1, 2, and 3 months after RT for patients treated in spinal regions vs. nonspinal bone regions, indicating RT relieved functional interference similarly in the two groups</p>

(Continued)

Table 3 (Continued).

Reference, Country	Design/Population	Patient-Reported Outcomes, Statistically Significant
Radionuclide therapy Nguyen et al (2011) ⁴³ Canada	<ul style="list-style-type: none"> Prospective cohort study in patients (N = 109) with painful spinal metastases from any cancer^a treated with palliative RT (EBRT) Median age, 68 years Radiation sites: thoracic/thoracic lumbar, n = 56; lumbar/lumbar sacral, n = 44; cervical/cervico-thoracic, n = 9 Worst pain at initial RT consultation using BPI: <ul style="list-style-type: none"> Mean, 7.57 Median (range), 8.0 (2-10) 	<ul style="list-style-type: none"> Significant decreases (improvements) from baseline to 3 months in BPI mean scores among all patients: <ul style="list-style-type: none"> Worst pain**** Average pain**** Current pain**** Interference <ul style="list-style-type: none"> General activity**** Mood**** Walking ability**** Normal work**** Relationships**** Sleeping**** Enjoyment of life**** Comparing BPI pain and interference mean scores change from baseline to 3 months in responders (all PRs) with nonresponders after adjusting for time^c: <ul style="list-style-type: none"> Mood**
Kurosaka et al (2012) ⁴⁶ Japan	<ul style="list-style-type: none"> Prospective, single-arm, open-label pilot study of patients (N = 13) with CaPBM from prostate cancer receiving ⁸⁹Sr <ul style="list-style-type: none"> All 13 had prior hormonal therapy 10 patients had castration-resistant prostate cancer Median age, 74 years n = 8 received EBRT to a symptomatic site of bone metastasis a median of 32.5 months (range, 9-149 months) before ⁸⁹Sr Concurrent systemic anticancer therapy: 23.1% received chemotherapy a median of 4 months (range, 3-12 months) before ⁸⁹Sr 	<ul style="list-style-type: none"> EORTC QLQ-BM22 subscales, significant changes in mean scores from baseline at 1, 2, and/or 3 months: <ul style="list-style-type: none"> Pain characteristics at 1* and 2* and 3 months** Functional interference at 1* and 2* and 3 months* Psychosocial aspects at 2** and 3 months**
Lange et al (2016) ⁴⁷ The Netherlands	<ul style="list-style-type: none"> Prospective observational study of patients (N = 81) with CaPBM from prostate cancer (n = 56) and breast cancer (n = 25) <ul style="list-style-type: none"> 61 patients returned their forms and were eligible for analysis Mean age, 73 years Previous treatment with RT (34%), radionuclide therapy with ¹⁵³Sm-EDTMP (18%), and surgery to bone lesions (3.4%), with time between these and ¹⁸⁸Re-HEDP not stated Mean VAS for pain before RT (SE): <ul style="list-style-type: none"> All, 5.9 (0.3) Prostate cancer, 5.7 (0.4) Breast cancer, 6.4 (0.4) 	<ul style="list-style-type: none"> Mean change in VAS^d from baseline to 1 and 2 months after ¹⁸⁸Re-HEDP <ul style="list-style-type: none"> All patients at 1* and 2 months* Prostate cancer at 1* and 2 months* Breast cancer at 1* and 2 months* QLQ-C30, GHS/QOL scores <ul style="list-style-type: none"> All patients at 1* and 2 months* Prostate cancer at 1 month* Breast cancer at 1 month*

Notes: ^aThe most common three cancers were breast, prostate, and lung. ^bBPI functional interference outcomes include general activity, mood, walking ability, normal work, relationship with others, sleeping, and enjoyment of life. ^cGeneral Linear Mixed Model with Bonferroni adjusted $P < 0.007$ for significance. ^dA decrease of at least 2 points on the VAS was considered clinically relevant. **** $P < 0.0001$; *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$.

Abbreviations: ¹⁵³Sm-EDTMP, samarium-153 ethylenediamine tetramethylene phosphonate; ¹⁸⁸Re-HEDP, rhenium-188 hydroxyethylidene diphosphonate; ⁸⁹Sr, radionuclide strontium-89; BPI, Brief Pain Inventory; CaPBM, cancer pain due to bone metastases; EBRT, external beam radiation therapy; EORTC QLQ-BM22, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Bone Metastases module; EORTC QLQ-C15-PAL, EORTC Quality of Life Questionnaire-Core 15 Palliative; EORTC QLQ-C30, EORTC Quality of Life Questionnaire-Core Module; GHS, Global Health Status; NR, not reported; PR, partial response; QOL, quality of life; RT, radiation therapy; SD, standard deviation; SE, standard error; VAS, visual analog scale.

metastases showed that there was no statistical difference in the pain improvement or functional difference between the two groups, indicating that RT improved functional interference scores similarly for patients with spinal and nonspinal bone metastases.⁴⁵ A separate study of palliative RT using radionuclide strontium-89 (⁸⁹Sr) to manage pain from spinal bone metastases found that 64% of patients experienced a PR after 3 months. Both psychosocial aspects and functional interference subscales improved by 2 months and remained improved by 3 months.⁴⁶

⁸⁹Sr was also able to reduce bone pain and improve HRQOL among 13 patients with prostate cancer and bone metastases for at least 3 months.⁴⁶ Although this study had a small sample size, it showed that radionuclide therapy not only reduced pain but improved QOL in patients with prostate cancer with painful bone metastases. Similar improvements in pain and HRQOL were reported in a separate study using palliative radionuclide therapy (¹⁸⁸Rhenium-hydroxyethylidene diphosphonate [¹⁸⁸Re-HEDP]) in routine clinical practice in patients with prostate or breast cancer and painful bone metastases.⁴⁷ In this study, pain palliation was assessed using a visual analog scale, and QOL was assessed using the EORTC QLQ-C30 GHS/QOL scale. Overall, 69% of patients experienced reduction in pain following treatment with ¹⁸⁸Re-HEDP while not increasing their opioid intake. The mean visual analog scale scores decreased across both subgroups at Weeks 4 and 8, while the mean GHS scores increased over the same period, indicating a reduction in bone pain and an increase in QOL, respectively.

One additional radiotherapy option for the management of mCIBP is brachytherapy with iodine-125 (¹²⁵I brachytherapy), an internal RT. Surgical implantation of brachytherapy seeds near metastatic lesions is guided by computed tomography. In several studies, the use of ¹²⁵I brachytherapy, which was occasionally performed in combination with other interventions like vertebroplasty, was able to reduce pain for patients with mCIBP for at least 24 weeks.^{48–50} One retrospective study that directly compared the outcomes for patients treated with EBRT or ¹²⁵I brachytherapy found that ¹²⁵I brachytherapy reduced pain scores on the Brief Pain Inventory and that it improved HRQOL.⁴⁸ Clinical studies conducted by Wang et al and Yang et al also found that ¹²⁵I brachytherapy reduced pain and improved HRQOL; Yang et al found that 98.0% of patients reported pain relief following ¹²⁵I brachytherapy.^{49,50}

Opioids

As previously mentioned, 60% to 80% of patients experience at least some pain relief after palliative RT, but only 30% experience complete pain relief following palliative RT.⁸ This leaves 20% to 40% of patients with no pain improvement from EBRT and another 30% to 50% with inadequate pain improvement. Analgesic options for cancer pain, including pain related to bone metastases, are based on the intensity of the pain. The drug classes considered for analgesia are NSAIDs, weak opioids, and strong opioids.³¹ Adjuvant therapies (eg, antidepressants, anticonvulsants, topical therapies) enhance the analgesic effects of other drugs and potentially allow for the reduction of analgesic doses.^{32,51} Relatively strong opioids (morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone) with or without nonopioid analgesics or adjuvants are used for severe and persistent pain.³² Strong opioids are recommended for patients with moderate to severe cancer pain, including cancer pain due to bone metastases.^{8,29,31} Breakthrough cancer pain may be treated with rapid-onset opioids like fentanyl formulations, although the prevalence of breakthrough cancer pain is still 59% even after these drugs are introduced.^{14,52,53} Methadone is effective against both nociceptive and neuropathic pain and has been formulated for multiple delivery routes, making it an attractive candidate for treating cancer pain due to bone metastases.⁵⁴ However, specific studies on methadone use on cancer pain due to bone metastases are lacking.

None of the studies identified in this targeted review assessed the impact of opioids on HRQOL in patients with cancer pain due to bone metastases. However, Table 4 summarizes the studies from this literature review that assessed whether patients with bone metastases were being treated appropriately for their pain level or cancer pain due to bone metastases. There is evidence for international underuse of opioids for cancer pain due to bone metastases. Two separate Canadian studies found that 25.8% to 48% of cancer patients with bone metastases were not prescribed adequately strong analgesics for their pain,^{55,56} and one of the studies found an increase in the proportion of patients undertreated over the study period (1999–2006).⁵⁵ A Portuguese study found even greater undertreatment of adults with self-reported metastatic bone pain, with 84% of patients with moderate to severe pain not treated with a strong opioid.⁵⁷ A multicountry study of analgesic and bone-targeting agent use in Europe found that 15% of patients with prostate cancer and moderate

Table 4 Opioid Treatment Patterns

Reference and Country	Design/Population	Patient-Reported Outcomes, Statistically Significant Results
Mitera et al (2010) ⁵⁵ Canada	<ul style="list-style-type: none"> Retrospective study conducted 1999–2006 N = 1000 with bone metastases referred to a Rapid Response Radiotherapy Program 	<ul style="list-style-type: none"> 25.8% of patients reported negative PMI^a Proportion of patients with negative PMI significantly increased over the study duration (14.8% in 1999 to 44% in 2006)
Kirou-Mauro et al (2009) ⁵⁶ Canada	<ul style="list-style-type: none"> Retrospective study conducted 1999–2006 N = 1038 with bone metastases referred to a Rapid Response Radiotherapy Program 	<ul style="list-style-type: none"> Most patients (range, 63–91%) experienced moderate to severe pain each study year 29–48% of patients were undertreated each year, defined as not receiving strong opioids for moderate to severe pain
Vieira et al (2019) ⁵⁷ Portugal	<ul style="list-style-type: none"> Conducted 2010–2011 N = 84 with bone-involved cancer who were receiving bisphosphonate therapy at a cancer center 	<ul style="list-style-type: none"> 62.8% of patients had moderate to severe pain Of the 49 patients reporting moderate to severe pain, 41 patients were treated with a weak opioid, a nonopioid, or no analgesic therapy
Body et al (2019) ⁵⁸ Multicountry (Europe ^b)	<ul style="list-style-type: none"> Cross-sectional survey conducted February–April 2015 using the Adelphi Prostate Cancer Disease-Specific Programme Physician-reported data for 3667 patients with prostate cancer, including 1971 with bone metastases 	<ul style="list-style-type: none"> Among 559 patients with moderate to severe pain from bone metastases: <ul style="list-style-type: none"> 288 (51.5%) were receiving strong opioids 271 (48.5%) were receiving weak opioids (33%), nonopioid analgesics (15%), or no analgesic (1%)
Decroisette et al (2011) ⁵⁹ France	<ul style="list-style-type: none"> N = 554 patients with lung cancer with bone metastases at 40 centers 	<ul style="list-style-type: none"> 387 patients (77.7%) received opioids

Notes: ^aPMI scores are derived from the pain score (0 for absence of pain, 1 for mild pain, 2 for moderate pain, and 3 for severe pain) and the analgesic use score (0 for non-analgesic, 1 for a nonopioid, 2 for a weak opioid, and 3 for a strong opioid). The PMI score is the analgesic score minus the pain score. For example, a patient with severe pain (score = 3) who was prescribed a nonopioid analgesic (score = 1) would have a negative PMI (1–3 = –2), indicating undertreatment of pain. ^bBelgium, France, Germany, Italy, Spain, and the United Kingdom.

Abbreviation: PMI, Pain Management Index.

to severe pain from bone metastases were receiving only nonopioid analgesics, and another 33% were not receiving strong opioids.⁵⁸ However, in a French study, analgesic use (89.9%) and, in particular, opioid use (77.7%) were common in patients with lung cancer and bone metastases.⁵⁹

Studies suggest that pain from bone metastases is more likely to be addressed when physicians are aware of the pain, such as following a skeletal-related event (SRE) or when cancer progresses after each successive line of therapy. A study with an international population of clinical trial participants with solid tumors found that the proportion of patients using strong opioids for moderate to severe pain remained relatively stable in patients who did not experience an SRE, whereas the proportion of patients using strong opioids increased in the 6 months preceding an SRE.⁶⁰

Other Pharmacological Interventions

Radiation therapy and opioids are the most commonly used and effective forms of pain control for cancer patients with bone metastases, but many patients receive other pharmacological interventions, including NSAIDs and bisphosphonates. By blocking osteoclast activity, bisphosphonates can prevent fractures and other SREs.³¹ A chart review study in Japan found that both bisphosphonate and pain medication use increased as their other treatments progressed from first-line therapy to fourth-line therapy, with significantly higher use of bisphosphonates, NSAIDs, and opioids in patients with symptomatic skeletal events compared with patients without symptomatic skeletal events.⁶¹ However, the evidence for an analgesic effect of bisphosphonates on bone pain is weak.⁸ The analgesic effects of bisphosphonates are modest, so other medications are needed as the primary agent for pain relief.²⁹ Similarly, evidence indicates denosumab delays the onset of pain but does not provide relief for established pain.^{8,62} Data from a systematic review by Hendriks et al⁶³ highlight the lack of high-level evidence showing that bisphosphonates or denosumab reduce pain or improve QOL in patients with non–small-cell lung cancer with bone pain. Of 13 studies of bisphosphonates or denosumab identified in the Hendriks et al⁶³ review, only five studies (in 6 reports) assessed QOL.^{64–69} Measures of QOL included the Functional Assessment

of Cancer Therapy-General (FACT-G), EORTC QLQ-C30, and Lung Cancer Symptom Scale. Only two of the five studies reported a significant improvement in QOL.^{66,69} Hendriks et al⁶³ concluded that the evidence that bisphosphonates or denosumab has an influence on QOL in patients with non-small-cell lung cancer and bone metastases is “very weak.”

Minimally Invasive and Surgical Interventions

A substantial proportion of the population with mCIBP has undertreated pain. Minimally invasive therapies (eg, epidural or intrathecal anesthesia, nerve blocks, ablative procedures, kyphoplasty, cementoplasty, and vertebroplasty) are an option when oral or injectable pharmacological therapies are not effective for persistent pain relief. Pain specialists may choose to use these minimally invasive, interventional treatments early in the pain treatment process or as complementary treatments alongside a standard pain management plan.⁹ However, minimally invasive, interventional therapies are currently underutilized.⁹ Minimally invasive procedures to strengthen bones weakened or fractured by the presence of metastases, including kyphoplasty and vertebroplasty, are recommended by several medical governing bodies to potentially improve QOL for patients with bone metastases.^{30,41,70,71} However, recent data on the impact of kyphoplasty or vertebroplasty on HRQOL are limited, and vertebroplasty is controversial, as studies on its efficacy in reducing mCIBP are mixed.^{72–75} A 2021 publication reported that, in patients with cancer pain due to bone metastases, pain was significantly reduced and HRQOL was significantly improved up to 6 months after either radiofrequency ablation alone or radiofrequency ablation with vertebroplasty.⁷⁶

Surgery is an option for serious complications of bone metastases, including restoration of function because of spinal instability or impending spinal instability and pain that is intractable or was not relieved by nonsurgical therapy.⁷⁷ Additionally, although surgical management of painful bone metastases improves patients’ functional outcome and pain as early as 2 weeks postoperatively, it does not appear to have any impact on HRQOL.⁷⁸ However, HRQOL is affected by several factors, including bone metastases, the operation procedures endured by the patients, other comorbidities, and adjunctive treatments; these may have limited the ability to detect differences in HRQOL resulting from surgery.⁷⁸

Discussion and Further Research

Although patients with bone metastases have limited longevity,⁷⁹ for many patients, cancer pain due to bone metastases impacts their QOL for months or even years. For some cancers, such as breast and prostate cancer, the median survival of patients with bone metastases is approximately 2 years.^{80,81} There is a great need for therapeutic options that can provide pain relief and improve emotional, social, and physical functioning and overall HRQOL.

As described in this review, pain relief and improvements in HRQOL have been demonstrated for substantial proportions of patients treated with RT, although the improvements may take time to manifest and then wane over subsequent months. For patients continuing to experience moderate to severe cancer pain after RT for bone metastases, the current nonsurgical strategy is to treat the patient with strong opioids. However, evidence on opioid treatment patterns by pain severity suggests that opioids are underutilized in this patient population. The studies of undertreatment for cancer pain due to bone metastases were not designed to determine why patients were undertreated. A thorough, systematic investigation of opioid treatment patterns in patients with mCIBP is warranted.

Likely explanations for underuse are stigma around opioid addiction, prescribing limitations, and opioid side effects. Side effects include severe drowsiness, dry mouth, dizziness, breathing difficulties, and constipation, with the constipation persisting throughout treatment.^{82–84} Although persistent constipation can now be medically managed,^{8,85} in the US, patients with legitimate need for opioids now face stigma, fear, and guilt for using opioids.⁸⁶ US patients also face access issues relating to pharmacy obstacles to filling prescriptions, insurance companies’ rules about types or amounts of medication allowed, and decreased manufacturing of opioids as a measure to limit inappropriate access.^{86,87} Outside the US in countries that did not experience an opioid crisis,^{88–90} physician and patient awareness and attitudes about pain and analgesics to control pain may still be contributing to the rise in undertreatment over time.⁵⁵ Additionally, the lack of opioid availability and socioeconomic factors in some countries may negatively impact access to health care and pain management.

Palliative care is known to improve the QOL of patients with advanced cancer, and opioids remain a backbone of cancer palliative care. Patients with prolonged access (greater than 4 weeks prior to death) to strong opioids as part of their end-of-life care were less likely to require emergency hospitalization and chemotherapy near the end of life.⁹¹ While opioid use poses a number of challenges, leading to a large push to find opioid alternatives, access to opioids is essential for adequate cancer pain treatment. Ensuring patients have access to sufficient care, whether that takes the form of radiation or pharmacological interventions, is critical to ensuring the most positive outcomes possible.

This literature review indicates that there is a significant gap in research on the impact of cancer pain due to bone metastases on patients' QOL. In particular, most studies of cancer pain due to bone metastases do not investigate the barriers to adequate pain management that can prolong patients' QOL. Additionally, our findings suggest that additional treatment strategies are needed to sufficiently manage cancer pain due to bone metastases.

Limitations of This Review

This literature review was focused specifically on pain related to bone metastases. Other recent reviews have described management of cancer pain, and these articles provide discussions of opioids and other pharmacological and nonpharmacological interventions regardless of the source of cancer pain.^{54,92–95} Because of the narrow focus of our review, studies of the effect of opioids on HRQOL were not identified, nor were studies of economic burden associated with cancer pain due to bone metastases. Few of the identified studies provided real-world treatment patterns for patients with mCIBP. Only a few treatment pattern studies addressed whether moderate to severe cancer pain due to bone metastases was being treated per guidelines. Our intent was not to compare opioid use across countries that may have different restrictions on opioid use.

The proportion of patients seen at radiation centers may be an overestimation of the undertreatment problem because patients with adequately controlled cancer pain due to bone metastases are not typically referred to these centers.^{55,56} However, studies of patients with bone metastases seen at oncology or medical centers do not have this selection bias, and this review identified non-radiation-center studies that also report undertreatment.^{57,58} None of the studies in this review were designed to determine the reason for undertreatment of their study populations.

Conclusions

Patients with mCIBP have lower HRQOL because of the impact of bone pain, in addition to other cancer symptoms, and our review found that these patients are globally undertreated for their pain. Radiation therapy for cancer pain due to bone metastases provides relief for many and improves HRQOL. However, a substantial proportion of patients obtain no relief from RT, and most others have incomplete relief. Strong opioids are recommended for those with moderate to severe cancer pain due to bone metastases. For many patients, RT fails to bring adequate relief and the use of opioids is often limited by side effects. This has created an ongoing unmet need for many patients with metastatic cancer-induced bone pain. Additional research is needed to determine patient preferences and physician attitudes regarding choice of analgesic for moderate to severe cancer pain due to bone metastases.

Abbreviations

¹²⁵I, iodine-125; ¹⁵³Sm, samarium-153; ¹⁸⁸Re-HEDP, rhenium-188 hydroxyethylidene diphosphonate; ²²³R, radium; ⁸⁹Sr, strontium-89; BPI, brief pain inventory; CI, confidence interval; CR, complete response; EBRT, external beam radiation therapy; EDTMP, ethylenediamine tetramethylene phosphonate; EORTC, European Organisation for Research and Treatment of Cancer; EORTC QLQ-BM22, EORTC-Bone Metastases module; EORTC QLQ-C15-PAL, EORTC Quality of Life Questionnaire Core-15 Palliative; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module; EORTC QLQ-MY20, EORTC Quality of Life Questionnaire Multiple Myeloma module; ESMO, European Society for Medical Oncology; FACT-G, Functional Assessment of Cancer Therapy–General; GHS, Global Health Status; HEDP, hydroxyethylidene diphosphonate; HRQOL, health-related quality of life; K6 distress scale = Kessler Psychological Distress Scale 6; mCIBP, metastatic cancer-induced bone pain; mCRPC, metastatic castration-resistant prostate cancer; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; PMI, Pain Management Index; PR, partial response; PROMIS, Patient-Reported Outcomes

Measurement Information System; QOL, quality of life; RT, radiation therapy; SD, standard deviation; SE, standard error; SLR, systematic literature review; SRE, skeletal-related event; UK, United Kingdom; US, United States; VAS, visual analog scale.

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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