REVIEW ARTICLE

Burden of skeletal-related events in prostate cancer: unmet need in pain improvement

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Abstract

Purpose Up to 75 % of patients with prostate cancer experience metastatic bone disease, which leads to an increased risk for skeletal-related events (SREs) including pathological bone fracture, spinal cord compression, and hypercalcemia of malignancy. Our objective was to systematically review the literature on the impact of SREs on quality of life (QOL), morbidity, and survival with a primary focus on the impact of SREs on pain in prostate cancer patients.
Methods We searched PubMed, limiting to peer-reviewed English-language human studies published in 2000–2010. The search was based on the US Food and Drug Administration and European Medicines Agency definition of an SRE, which includes pathologic fracture, spinal cord compression (SCC), hypercalcemia of malignancy, and radiotherapy or surgery to bone resulting from severe bone pain.
Results A total of 209 articles were screened, of which 173 were excluded, and 36 were included in this review. Patients with SREs had more pain and worse survival compared with no SREs. Pathologic bone fractures worsened QOL and were associated with shorter survival. Radiation therapy of SCC alleviated pain and improved morbidity. SCC was associated with decreases in patient survival. Radiation therapy and surgery to bone improved pain.

Conclusions Specific SREs are associated with worse outcomes, including increased pain, poorer QOL, morbidity, and survival. Treatment of SREs is associated with improved pain, although there remains a need for more effective treatment of SREs in prostate cancer patients.

Keywords Prostatic neoplasms · Bone neoplasms ·
Fractures · Bone · Spinal cord compression · Radiotherapy ·
Pain · prostate cancer · metastatic bone disease ·
bone metastases · skeletal-related events

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Introduction

Prostate cancer is the second most commonly diagnosed cancer type and the second leading cause of cancer death among American men. In 2014, an estimated 233,000 men will be diagnosed with, and 29,480 men will die of, prostate cancer in the USA [1]. Increased prostate-specific antigen screening has resulted in higher numbers of patients being diagnosed during the early locoregional stages, when the disease is relatively indolent and asymptomatic [2]. Patients with metastatic prostate cancer present with significant symptom burden, and those with distant metastases at diagnosis have only a 28 % relative survival rate [3, 4].

Advanced prostate cancer preferentially metastasizes to the bone [5]. Although the prevalence of bone metastasis has not been well characterized, it has been estimated that 65–75 % of patients with advanced prostate cancer will develop metastatic bone disease (MBD) [6]. MBD results in weakened structural integrity of the bone, and cancer patients with MBD invariably have an increased incidence of skeletal-related events (SREs) [7]. Among patients diagnosed with bone metastases, skeletal morbidity is evaluated by the occurrence of SREs such as pathological bone fracture, spinal cord compression, hypercalcemia of malignancy, and severe bone pain requiring

palliative radiation therapy (RT) or surgery, as described by the US Food and Drug Administration (FDA) [8] and European Medicines Agency (EMA) [9]. Although MBD may be diagnosed in patients with a variety of cancer types, about 80 % of all cases of MBD occur in patients with breast or prostate cancer [6, 7].

Almost 3 % of prostate cancer patients have bone metastases at diagnosis, of whom 43.6 % experience an SRE during follow-up [10]. SREs appear to be associated with significant morbidity and economic burden, and SREs are linked to decreased survival. Nørgaard et al. [10] reported 5-year survival of prostate cancer patients is 56 % without bone metastasis, 3 % with bone metastasis, and 0.7 % in those with bone metastasis and SREs.

To gain a comprehensive overview of the burden of SREs, we systematically reviewed the literature on the impact of SREs on pain, quality of life (QOL), morbidity, and survival in patients with cancers of the prostate, breast, lung, and kidney and multiple myeloma. In this review, we summarize our results for prostate cancer, with a primary focus on the impact of SREs on pain.

METHODS

We searched PubMed for peer-reviewed English-language human studies published in 2000–2010. The search was based on a definition of an SRE accepted by the FDA and EMA. Search strategy key terms included "fracture," "spinal cord compression," "hypercalcemia," "skeletal related events," "metastatic bone cancer," "radiation therapy," "bone surgery," "skeletal surgery," "spine surgery," and "bone pain" in "prostate cancer," "renal cancer," "multiple myeloma," "lung cancer," or "breast cancer." Given the aims of this study, we only summarize results in prostate cancer.

Articles were included if they were randomized controlled trials (RCTs), clinical trials with a control group, systematic reviews, meta-analyses, case series, or economic analyses. All RCTs were quality-rated using the Jadad scale. When we found several systematic reviews for a given topic, we selected the one which fulfilled the following criteria: most recent review, highest quality rating, largest number of RCTs and patients included, and availability of a meta-analysis. Articles were excluded if they did not provide interpretable results on outcomes of interest. Although radionuclide therapy (RNT) is not part of the FDA- or EMA-accepted definition of an SRE, studies of RNT that were identified under the "radiation therapy" key terms in our systematic search were not excluded from our review. Review was conducted by two independent reviewers.

In our summary of the literature, we address clinical SREs and treatment of SREs. Clinical SREs included pathological bone fracture, spinal cord compression, and hypercalcemia of malignancy. Treatments of clinical SREs included RT and surgery to bone.

To insure inter-rater reliability and robustness of data abstraction, two reviewers initially and independently reviewed and abstracted data from 10 identified studies. The reviewers agreed on 9 out of 10 articles and disagreed on a single article. Full agreement was met after further discussion. The rest of the articles were divided between the two reviewers, and they abstracted the data.

Results

The literature search yielded a total of 209 articles (Fig. 1). After screening these articles, 136 did not meet the inclusion criteria. Thirty-six of the 73 remaining articles included prostate cancer patients and were summarized in this review.
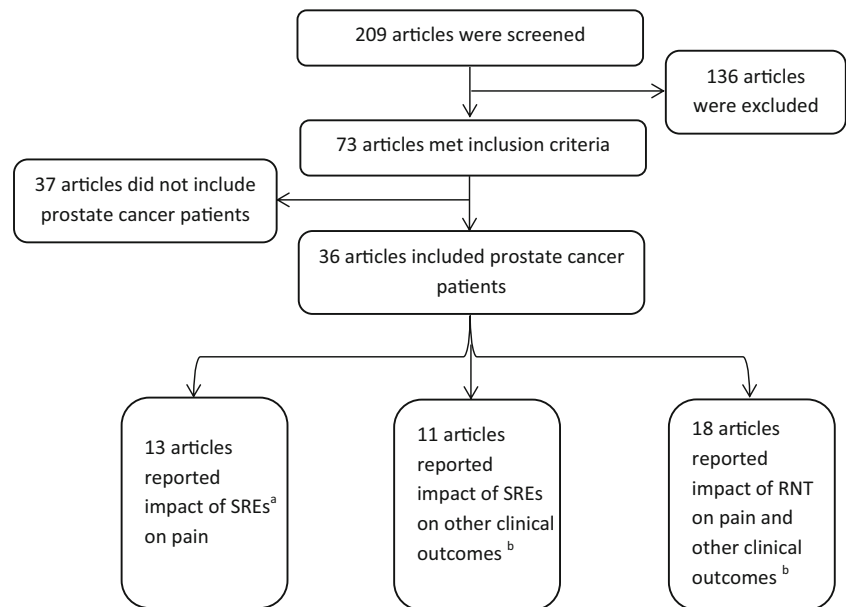
Impact of SREs on pain

A variety of measures of pain, including visual analogue scale (VAS), brief pain inventory (BPI), opioid use, and analgesic scores, were used in the studies included in this review. We summarized these results descriptively rather than meta-analytically (Table 1). Three articles described the impact of SREs as a group on pain [11–13], three articles presented the impact of specific clinical SREs on pain [13–15], and eleven articles examined the impact of specific treatments of clinical SREs on pain [13–23].

Impact of SREs as a group on pain

Saad et al. [12] conducted a randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. This study demonstrated a statistically significant reduction in the rate of fractures as well as other SREs in patients receiving zoledronic acid compared with placebo. Despite a reduction in SRE frequency, there were no statistically significant differences in analgesic scores between groups. Two studies [11, 13], both post-hoc analyses of a bisphosphonate trial [12], specifically addressed the impact of SREs on pain in patients with prostate cancer and bone metastases. Weinfurt et al. [13] examined only patients who experienced an SRE during the 96-week trial. For this analysis, SREs were grouped into three categories: radiation to bone, pathologic fractures, and other SREs. Pain intensity, assessed by the BPI, declined after radiation but not after other SREs. Similarly, DePuy et al. [11] reanalyzed the Saad et al. [12] trial data to ascertain the magnitude of decrease in pain among patients with multiple SREs. Patients with at least one SRE during the 182-day landmark period showed a significantly larger increase in pain in the subsequent year as measured by the BPI. Overall, these findings

Fig. 1 Studies on the impact of skeletal-related events in prostate cancer. Skeletal-related events (*SREs*), radionuclide therapy (*RNT*). *Superscript letter a* includes clinical SREs (pathological bone fracture, spinal cord compression, and hypercalcemia of malignancy) and treatment of clinical SREs (radiation therapy and surgery to bone). *Superscript letter b* other clinical outcomes include quality of life, morbidity, and survival

reveal a profound negative impact of SREs on pain in patients with bone metastases.

Impact of specific clinical SREs on pain

There were no studies on the impact of hypercalcemia on pain. As previously described, Weinfurt et al. [13] examined the burden of pain associated with grouped SREs, which included a pathologic bone fractures group. There were no changes in pain intensity or pain interference as measured by the BPI after fractures in this study. Another study measured pain levels before and after treatment of spinal cord compression (SCC) [14]. In this study, 49 men with prostate cancer, symptomatic SCC, and/or nerve root compression due to metastases were treated with RT. Pain decreased after RT. The percentage of pain-free patients increased from 2 % before RT to 11 % after RT. The proportion of patients with pain "often and all the time" decreased from 50 % before to 15.6 % after RT. At 2 and 6 months post-RT, most patients who were taking analgesics had no pain or only intermittent pain. Van der Linden et al. [15] studied 342 patients who had prostate (24 %) or other malignancies with painful spinal metastases and who were treated with RT. Seventy-three percent of patients in this study responded with lesser pain after treatment.

Impact of specific treatments of clinical SREs on pain

Several studies assessed the impact of RT on pain. Up to 73 % of patients had some pain relief response [13, 15, 18, 19, 23], 46–76 % had partial/complete pain relief [14, 16, 18, 19, 22], and 1–47% had complete pain relief [16–23].

Salazar et al. [22] compared three schedules of RT delivery in 156 patients with prostate (32 %) and other cancers, and found 91 % of patients responded to therapy within 3–8 days post-RT: 45 % of patients had complete and 46 % had partial pain relief, and 9 % had no response. Weinfurt et al. [13] reanalyzed trial data reported by Saad et al. [12] on 248 patients who experienced an SRE during the 96-week trial and demonstrated decreased pain intensity on the BPI after radiation treatment but not after other SREs (pathologic fracture, spinal cord compression, surgery to bone, or a change in antineoplastic therapy to treat bone pain). Hartsell et al. [18] and Hamouda et al. [17] conducted RCTs to compare single versus multifractionated RT in patients with painful bone metastases. Hartsell et al. [18] evaluated pain relief at 3 months post-RT with the BPI and reported 17 % (95) of patients achieved complete pain relief and 49 % achieved partial pain relief, for an overall response rate of 66 %. Hamouda et al. [17] assessed pain relief by the VAS and reported the maximum benefit was achieved at 8 weeks post-RT: 86 % (88) of 102 patients experienced a reduction in their pain and 47 % had complete pain relief. Overall, prostate cancer had the highest response rate (100 %) compared with other cancers at 8 weeks after radiotherapy. Sze et al. [23] conducted a systematic review of RCTs on the effects of single fraction versus multifraction RT for malignant bone pain relief in patients with prostate and other cancer, and estimated an overall pain response rate of 59 % (in 3548 patients form 11 trials) and complete pain response rate of 33 % (in 2876 patients from 7 trials). Hird et al. [19] studied the incidence of pain flair among 111 patients with prostate (22 %) or other cancers with bone metastases treated with radiotherapy, and demonstrated that 25 % of patients with primary prostate cancer experienced pain flare. Pain flair was associated with an increase in analgesic intake and only a minimal increase in pain level. Overall pain relief response at 6 weeks post-RT

Table 1 Impact of skeletal-related events on pain in metastatic to the bone prostate cancer patients

Reference	SREs	Number of patients	Pain measure	Impact on pain (assessed based on pain measure)
Aass 2005 [14]	RT of SCC	49 prostate cancer patients	Barthel ADL Index, analgesic consumption	Post-RT for SCC, pain decreased: proportion of pain-free patients increased from 2 % (1/49) pre-RT to 11 % (5/45) post-RT and patients with pain "often and all the time" decreased from 50 % pre-RT to 15.6 % (7/45) post-RT.
Berg 2009 [16]	RT	44 (41 prostate cancer) patients	QLQ-C30, analgesic consumption	At 4 weeks post-RT, 76 % (26/34) of patients reported partial or complete relief and 8.8 % (3) had complete pain relief. Complete pain relief culminated at week 16 with 24 % of patients being pain-free.
DePuy 2007 [11]	As a group	471 prostate cancer patients	BPI	Patients with at ≥1 SRE in the 182 day landmark period had a significantly larger increase in pain in the subsequent year.
Hamouda 2007 [17]	RT	107 (18 prostate cancer) patients	10-point VAS	Maximum benefit was achieved at 8 weeks post-RT 86 % (88/102) of patients had reduced pain and 47 % (48) had complete pain relief; overall, prostate cancer patients had the highest response rate (100 %) compared with other cancers.
Hartsell 2005 [18]	RT	898 breast and prostate cancer patients (445 male)	BPI	At 3 months post-RT, 17 % (95/573) of patients achieved complete pain relief and 49 % (280) achieved partial pain relief, for an overall response rate of 66 % (375); 10 % (55) of patients had progression of pain.
Hird 2009 [19]	RT	111 (24 prostate cancer) patients	BPI, analgesic consumption	At 6 weeks post-therapy, 1 % (1/72) of patients achieved complete pain relief, 65 % (47) achieved partial response, 25 % (18) had stable disease, and 8 % (6) had progression of disease. Overall pain relief response was in 67 % (48) of patients.
Saad 2002 [12]	As a group	643 prostate cancer patients	BPI, analgesic score	Despite a reduction in SRE frequency, there were no statistically significant differences in analgesic scores between zoledronic acid versus placebo groups.
Salazar 2001 [22]	RT	156 (50 prostate cancers) patients	Pain severity frequency	Within 3–8 days post-RT, 91 % of patients responded to therapy (45 % had complete relief and 46 % had partial pain relief) and 9 % had no response.
Sze 2008 [23]	RT	Mainly prostate, breast, and lung	Various	Overall pain response rate was 59 % of 3548 patients from 11 trials and complete pain response rate was 33 % from 2876 patients from 7 trials.
Van der Linden 2005 [15]	RT of SCC	342 (82 prostate cancer) patients	11-point pain scale	After RT, 73 % of patients responded with lesser pain.
Weinfurt 2005 [13]	As a group	248 prostate cancer patients	BPI	Patients had declines in pain intensity after RT but not after other SREs.
Ibrahim 2008 [20]	Bone surgery	223 (29 prostate cancer) patients	Not specified	Majority of patients (92 %) had pain at presentation; post-surgery, 71 % had improved pain control, 11 % had no change, and 18 % experienced a worsening in their pain.
Liberman 2009 [21]	Bone surgery	31 (5 prostate cancer) patients	VAS, analgesic consumption	At 3-month post-surgery, 72 % (18/25) of patients had a reduction in pain, of which 50 % (9) had a VAS=0; 36 % of patients had a complete response, 36 % had a partial response, 4 % had a progression in pain, and 24 % experienced no response to treatment.

Barthel ADL Index Barthel Activities of Daily Living Index, *BPI* brief pain inventory, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, *VAS* visual analogue scale

occurred in 67 % of patients regardless of pain flair, which included 1 % of patients who had a complete pain relief response and 65 % of patients who had a partial response. Berg et al. [16] studied the effects of half-body irradiation (HBI) in 44 patients with multiple bone metastases from prostate (93 %) and other cancers. Maximum pain relief was achieved at 4 weeks after RT, where 76 % (26) of patients reported partial or complete relief and 8.8 % had complete pain relief. Complete pain relief culminated at week 16, with 24 % of patients being pain-free.

Two studies assessed the impact of bone surgery on pain [20, 21], indicating that 71–72 % of patients experienced some pain relief, 11–24 % had no pain relief, 4–18 % had worsening of pain, and 67 % had a reduction in opioid use [20, 21].

Ibrahim et al. [20] addressed the impact of spinal surgery on pain in 223 patients with prostate (13 %) and other cancers. The majority of patients (92 %) had pain at presentation; following surgery, 71 % had improved pain control, 11 % had no change, and 18 % worsened. A small study by Liberman et al. [21] assessed the impact of magnetic resonance-guided focused ultrasound on pain in 31 patients with painful bone metastatic lesions. At 3-months post-surgery, 72 % (18/25) of patients had a reduction in pain, of which 50 % (9) had a VAS score of 0; 36 % of patients had a complete response to treatment, 36 % had a partial response, 4 % had a progression in pain, and 24 % experienced no response to treatment.

Impact of SREs on quality of life, morbidity, and survival

Three bisphosphonate trials reported patients with SREs had worse QOL and survival than those without (Table 2) [11–13]. Among five studies that examined the impact of individual clinical SREs, two reported pathologic bone fractures decreased QOL and increased risk of death [13, 24] while SCC decreased survival and treatment of SCC reduced morbidity [14, 15, 25]. Other studies suggested RT may improve QOL [13, 16, 22]. Another study compared post-surgery survival and functioning in patients with spinal metastases [20]. We did not identify any studies on the impact of hypercalcemia on QOL, morbidity, or survival.

Saad et al. [12] conducted an RCT of zoledronic acid in 643 patients with prostate cancer. Zoledronic acid reduced the rate of fractures as well as other SREs as compared with the placebo. Despite a reduction in the SRE frequency, there were no differences in QOL (as measured by the Fundamental Assessment of Cancer Therapy General Scale [FACT-G] questionnaire), in morbidity (as measured by Eastern Cooperative Oncology Group [ECOG] performance status), and in analgesic scores between the zoledronic acid and placebo groups. DePuy et al. [11] reanalyzed trial data from this study to quantify the longitudinal effects of multiple SREs on QOL and survival. The investigators determined that patients with no SREs had higher QOL than those with any SREs and patients with one SRE had higher QOL than those with multiple SREs, as measured by the FACT-G total score and the emotional, functional, and physical well-being subscales. Similarly, patients with no SREs had better survival than those with one or multiple SREs (51.3, 29.8, and 22.4 %, respectively), and patients with at least one SRE showed a larger increase in pain as measured by the BPI. Weinfurt et al. [13] analyzed bisphosphonate trial data of 248 prostate cancer patients who experienced an SRE during a 96-week trial. SREs were grouped into radiation to bone, pathologic fractures, and other SREs (spinal cord compression, surgery to bone). Pathologic fractures were associated with declines in two of five FACT-G scores (physical and emotional well-being) and in two other measures of QOL (EuroQol VAS and EuroQol utility, which contains a pain/discomfort dimension). Radiation to bone had the broadest negative impact compared with other SRE categories, resulting in declines in the four of five FACT-G scores: total score and in physical, functional, and emotional well-being. Substantial declines in pain intensity and QOL were also seen in the mean BPI, EuroQol utility, and EuroQol VAS scores after RT. The negative effects of RT on QOL, despite the alleviation of bone pain, may reflect adverse effects of RT, repeated hospital and office visits required for treatment, and other effects (e.g., psychological) of radiation not captured in this study.

Saad et al. [24] analyzed RCTs of zoledronic acid to assess the effect of pathologic fractures on survival of 3049 patients with MBD from multiple cancer types. In prostate cancer patients who had an on-study fracture, 69 % (84/122) died by the end of the 2-year trial, compared to 71 % (366/518) of patients who did not have an on-study fracture. Pathologic fractures were associated with a 29 % increased risk of death in unadjusted analyses and a 20 % increased risk adjusted for prior SREs and baseline ECOG score.

Van der Linden et al. [15] examined 342 patients with prostate (24 %) and other malignancies with painful spinal metastases treated with RT, and reported a median survival of 1 month after diagnosis of SCC. Post-RT, prostate cancer patients had an overall median survival of 9.2 months, and those patients (multiple cancers) whose pain responded to RT had a better survival compared with nonresponders (median survival, 8.1 vs. 3.4 months). Hartsell et al. [18] evaluated the effect of RT for the palliation of painful bone metastases due to breast and prostate cancers, and reported that median survival ranged from 9.1–9.5 months, with overall survival of about 41 % at 1 year and 22 % at 2 years. Aass et al. [14] and Rades et al. [25] examined the impact of treatment of SCC with RT on morbidity and reported estimates of patient survival after treatment in 49 and 281 prostate cancer patients,

Table 2 Impact of skeletal-related events on clinical outcomes in prostate cancer

Quality of life	Morbidity	Survival
Impact of SRE as a group		
• Worse QOL on FACT-G [11] • May be worse QOL on FACT-G and EuroQol [13] • No difference in FACT-G between Tx and placebo groups with reduction in SREs [12]	• Despite reduction in SREs, no difference in ECOG PS between Tx and placebo groups [12]	• Patients with no SREs had greater 1-year survival than patients with SREs (49.7 vs. 28.2 %) [11]
Impact of bone fracture		
• Decline in physical and emotional well-being (FACT-G) and in EuroQol utility and VAS scores after pathologic fractures [13]	• No data	• Pathologic fractures associated with increased risk of death [24]
Impact of spinal cord compression		
• No data	• Improved Barthel score and ECOG PS with treatment of SCC [14, 25]	• Decreased survival in prostate cancer patients compared with similar patient cohorts [14, 25]
Impact of radiation therapy		
• Declines in 4 of 5 FACT-G scores and EuroQol utility and VAS scores after RT [13] • No improvement in EORTC QLQ-C30 nausea and fatigue [16] • Improvement in %NPR after HBI [22]	No data	• Those who achieved complete pain relief had better survival than those who responded partially [22]
Impact of bone surgery		
• No data	• Better functional improvements with excision than palliative surgery for SCC [20]	• Better survival with excision than palliative surgery for SCC [20]

Barthel ADL index Barthel activities of daily living index, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, *FACT-G* Fundamental Assessment of Cancer Therapy General Scale, *HBI* half-body irradiation, *SCC* spinal cord compression, *RT* radiation therapy, *Tx* treatment group, *VAS* visual analogue scale, *%NPR* percent net pain relief

respectively. Aass et al. [14] reported improvements after RT on the modified Barthel Activities of Daily Living Index. The proportion of patients fully dependent on assistance for mobility decreased from 69 % (34/49, baseline) to 36 % (9/25, 2 months after RT) and to 11.8 % (2/17, 6 months). Patients improved in their daily activities related to grooming, dressing, feeding, and toilet use. The improvement of morbidity in this study correlated with decreased pain levels after RT. In another study [25], improvement of motor function was observed in 33 % (92/281) of patients, no change in 53 % (150), and deterioration in 14 % (39) post-therapy. Of the 120 (43 %) patients who were nonambulatory before therapy, 33 % (40) regained the ability to walk. Median survival in this cohort was 17 months after SCC treatment with RT. Although other studies have reported that median survival of SCC patients ranges from 2 to 6 months [25], it is difficult to ascertain from this study the magnitude of benefit (if any) of RT for SCC due to prostate cancer on survival.

In a study on the effects of half-body irradiation (HBI) on QOL in 44 cancer patients (41 with prostate cancer), there were no significant improvements in the global QOL score or in the vomiting, diarrhea, or fatigue as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) symptom scales during 2 to 24 weeks postradiotherapy [16]. Salazar et al. [22] examined the impact of HBI on QOL, assessed by the percent of the remaining life free of pain (percent net pain relief: %NPR), in 156 patients with breast (n=72), prostate (n=50), and other cancers. After RT, average %NPR for all patients was 71 %, indicating that on average patients lived 71 % of their remaining lifetime pain-free. Percent net pain relief was 74 % in prostate cancer patients, which was higher than that in patients with breast cancer and cancers other than lung cancer. There was also a significant shift post-therapy towards best of the categories on performance status. Those who achieved complete pain relief had better survival than those who responded partially.

Ibrahim et al. [20] reported estimates of survival based on an investigation of the impact of spinal surgery on QOL, in terms of pain control and function, in patients with spinal metastases due to prostate and other cancers. Post-surgery, median survival was 11.7 months, with a 52 % 1-year and 35 % 2-year survival. Patients who had excision had better median survival than those that were in the palliative surgery group: 18.8 months for the en bloc group, 13.4 months for the debulking group, and 3.7 months for the palliative surgery group. The number of bed-bound patients decreased from 18 to 5 % post-surgery and 47 % of patients functionally improved on the Karnofsky Performance Scale. Similar to survival results, functional improvements were better for patients who underwent excision. The authors inferred that surgical treatment was effective in improving QOL by providing better pain control and enabling patients to regain or maintain mobility.

Impact of radionuclide therapy on pain and other clinical outcomes

Although radionuclide therapy is not part of the FDA- or EMA-accepted definition of an SRE, it is a treatment of SREs and impacts clinical outcomes of interest [26]. In his recent review, Tomblyn [26] concluded that targeted bone-seeking radionuclides are underutilized but are safe and effective in palliative treatment of diffuse osteoblastic metastases from solid tumors. In our review, we identified seventeen studies that examined the impact of RNT on pain in prostate cancer patients (Table 3) [27–43]. Overall, about 50–80 % of patients had an improvement in pain, 15–36.7 % had excellent or complete pain relief, 19–24 % had no pain relief, and 12–37.7 % experienced a worsening in their pain after treatment with RNT. Reductions in opioid use or analgesic scores were also reported in these studies. A few of these studies also reported RNT improved QOL [41,44], morbidity [27, 31–34, 40], and survival [29, 30, 45].

Discussion

Our literature review shows that clinical SREs are associated with worse clinical outcomes, including increased pain, poorer QOL, greater morbidity, and reduced survival. Pain can be reduced in patients with prostate cancer metastatic to bone by treating the cancer, which reduces the occurrence of SREs, and by treating SREs. Although treatment of SREs is associated with decreased pain and possibly with improved QOL, this review indicates that there remains a need for more effective treatment of SREs in prostate cancer patients. We also find that, to more accurately capture the burden of cancers metastatic to bone, consideration should be given to including RNT as an SRE since the indication and impact of this treatment is similar to RT in the palliative treatment of metastatic bone lesions.

Based on this review, about 70 % of patients experience some relief in pain after treatment with RT or bone surgery. Up to 24 % of patients may still achieve no relief and continue to experience pain and for up to 18 % of patients the pain may worsen [20, 21]. Malignant bone pain is a major determinant of QOL [46, 47] and is associated with shorter survival [48, 49]. Studies have also highlighted a potentially negative impact of pain on morbidity. Fulfaro et al. [50] demonstrated an improvement in both mean VAS score and ECOG PS after treatment with zoledronic acid in patients with bone metastases due to prostate cancer. It is evident that improving palliation of malignant bone pain is necessary to relieve the burden of MBD and to improve overall well-being of prostate cancer patients with MBD.

Table 3 Impact of radionuclide therapy (RNT) on pain in metastatic to the bone cancer patients

Reference	Number of patients	Pain measure	Impact on pain (assessed based on pain measure)
Bączyk 2007 [27]	60 prostate cancer patients	10-point VAS	Two months post-therapy, results were: unsatisfactory 20 %, partial effect 43.3 %, and complete effect 36.7 % of 60 patients.
Dafermou 2001 [28]	610 prostate cancer patients	Pain index, dosage of analgesic drugs	Patients were followed up for a period of 3–24 months, results were: no response 19 %, mild response 21.3 %, good response 33.3 %, excellent response 26.4 % of 610 treatment cases.
Fizazi 2009 [29]	43 prostate cancer patients	100-point VAS	Patients were followed for 3–30 months. The pain response rate was 69 % (20/29 patients). Among all treated patients, 76 % (32/42) had a 20 % decline in the pain level from baseline.
Han 2002 [30]	79 prostate cancer patients	100-point VAS, daily activity score, medication index	The mean VAS and daily activity scores improved post-treatment over 1–6 weeks of follow-up in the treated group but worsened in the placebo group. Overall, 65 % (28/43) of treated patients were responders vs. 36 % (13/36) in placebo group.
Liepe 2003 [31]	27 prostate cancer patients	100-point VAS, analgesic consumption	Post-therapy, pain relief (≤25 % on the VAS at least in two consecutive weeks without increase of analgesics intake) was achieved in 76 % (19/25) of patients; of which 20 % (5/19) of patients were pain-free.
Liepe 2005 [33]	64 (52 prostate cancer) patients	10-point VAS, analgesic consumption	Post-therapy, pain relief was achieved by 73 % (47/64) of patients and 16 % (10/64) were able to discontinue their analgesics and were pain-free.
Liepe 2005 [32]	46 (34 prostate cancer) patients	10-point VAS, analgesic consumption	Post-therapy, pain relief was achieved in 76 % (35/46) of patients, and there were no differences of pain palliation between prostate and breast cancer patients. Overall, 15 % (7/46) of patients were able to discontinue their analgesics and were pain-free
Liepe 2007 [34]	79 (61 prostate cancer) patients	10-point VAS, analgesic consumption	Post-therapy, pain relief was achieved by 73 % (58/79) of patients and 15 % (12/79) were able to discontinue their analgesics and were pain-free.
Nilsson 2005 [35]	25 (15 prostate cancer) patients	EORTC QLQ-C30	At 1-week post-therapy, 52 % had improvement, 36 % were unchanged, and 12 % had a worsening in pain. At the 4-week point, 60 % reported improvement, 20 % unchanged, and 20 % worse pain. At the 8-week point, 56 % reported improvement, 24 % unchanged, and 20 % worse pain.
Nilsson 2005 [36]	35 prostate cancer patients	0–4 verbal rating scale, 1–4 pain frequency scale	Pain intensity and pain frequency were reduced at 3–12 weeks post-therapy compared to baseline and were especially lower at 3, 6, and 9 weeks.
Palmedo 2003 [37]	64 prostate cancer patients	10-point VAS, medication index	Pain palliation was achieved in 74 % (41/55); >50 % of patients reported pain relief 3 months post-therapy. In the 41 responding patients, both the VAS and the medication index decreased post-therapy.
Sartor 2004 [38]	152 prostate cancer patients	Daily pain diaries, analgesic consumption, 100-point VAS, pain descriptor scale	Opioid consumption was reduced at 2 to 4 weeks post-treatment, and there were also significant reductions in pain on the VAS and pain descriptor scales.
Sartor 2007 [39]	202 (155 prostate cancer) patients	BPI	Post-therapy, a clinically significant pain decrease was observed in about 50 % of patients.
Tripathi 2006 [40]	86 (31 prostate cancer) patients	10-point VAS, analgesic score	Mean VAS scores and oral analgesic intake decreased post-therapy. Post-therapy, 80 % (25/31) of prostate cancer patients had a pain response: 16 % (5/31) achieved complete pain relief and 64.5 % (20/31) achieved partial response; 19.3 % (6/31) did not respond to treatment.
Turner 2001 [41]	93 prostate cancer patients	RTOG, analgesic consumption	Over 3 months post-therapy, 17.6 % (15/85) of patients experienced a complete pain response (no analgesics required), 23.5 % (20) had a moderate response, 21.2 % (18) had a minimal response, and 37.7 % (32) had a stable/worsening of pain. Overall response was 62.4 % (53/85) of patients.
Yaneva 2005 [42]	87 (27 prostate cancer) patients	3-point pain scale	Pain intensity improved post-therapy. At 1-month post-therapy, 67.8–70 % of patients had moderate pain and 30–32.2 % had slight pain.
Zafeirakis 2010 [43]	36 prostate cancer patients	Pain score index, analgesic consumption	Pain response occurred after 28/36 treatments (77.8 %), including a mild response in 22.2 % (8) of patients, a good response in 36.1 % (13) of patients, and an excellent response in 19.5 % (7) of patients; 22.2 % (8) of patients had no response.

BPI brief pain inventory, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, *VAS* visual analogue scale

This review revealed that including only RT and bone surgery as part of the definition of SREs may inappropriately exclude RNT, a common treatment similar to RT that impacts clinical outcomes of interest. The overall impact of SREs on pain, quality of life, morbidity, and survival, would be even larger if RNT was included in the definition of SREs, particularly since 18 of 36 reviewed studies were on the impact of RNT. Similar to RT and bone surgery, studies reported up to approximately 80 % improvement in pain [40] as well as improvements in QOL, morbidity, and possibly survival post-treatment. A notable proportion of patients continue to suffer from pain, indicating a need for more effective treatment of this debilitating symptom of SREs.

This review revealed significant gaps in literature. We only identified one study on the impact of pathologic bone fractures on pain and none on morbidity. No studies were found that assessed the impact of spinal cord compression on QOL. Overall, there were no studies on the impact of untreated spinal cord compression on outcomes of interest. We also did not identify any studies on the impact of hypercalcemia on pain, QOL, morbidity, or survival. There were no studies that compared survival of patients treated with XRT or bone surgery to those that did not receive these treatments or to those that were treated with other methods, preventing the estimation of a direct impact of treatment on patient survival. Consequently, future research focusing on these topics could substantially improve our understanding of the burden of MBD in prostate cancer patients.

Strengths and limitations

A strength of this review was the systematic and exhaustive approach used to search, examine, and summarize extensive results on the impact of SREs on several important outcomes in patients with MBD from prostate cancer that are available in the current peer-reviewed published literature. Some of the specific strengths of our approach include searching a major database in the last 10 years using a comprehensive search strategy, consisting of multiple key clinical and economic outcomes, and verification of inter-rater reliability and robustness of data abstraction by two independent reviewers. In this review, we were also able to determine current gaps in the literature, such as lack of published data on the impact of hypercalcemia of malignancy on outcomes of interest. Finally, the finding that nearly 50 % of articles included in this review were on the impact of RNT underscores the importance of considering this common treatment for MBD when making conclusions about the impact of SREs on pain. Importantly, this study demonstrated a continued unmet need in complete palliation of pain.

This study has limitations typical to literature reviews. The articles included in this review varied in methods, such as differences in patient samples examined, duration of follow-up, types of SREs examined, as well as differences in measures used to assess QOL, morbidity, and pain. Given a variety of measures are used to assess pain, future research should examine the impact of skeletal-related events on pain in metastatic to the bone prostate cancer patients while considering the sensitivity and specificity of these measures. Such variability in study methodology leads to difficulty in synthesis of results across studies and does not allow for meta-analyses. This review is further limited by the lack of summary on studies of denosumab [51], which was recently approved for the prevention of SREs in patients with bone metastases from solid tumors, since such articles were published after the completion date of this systematic search. There are other novel agents emerging as treatment options for metastatic prostate cancer with a primary end point of pain palliation or pain response, such as the ones evaluated in a phase III trials: NCT01083615 and NCT01522443 [52]. Given these recent changes and ongoing expansion in the therapeutic options for metastatic prostate cancer, future research should entail a summary of the impact of SREs on pain in context of therapies not included in this review.

We systematically reviewed the literature on the impact of SREs on pain and other clinical outcomes in patients with prostate cancer, so our review did not entail a review of literature on measurement properties or psychometric validation of available measures of pain in cancer. Prior reviews examined the various patient-reported outcome (PRO) measures used to assess pain in cancer (e.g., Matza 2012; Clark 2014). Matza et al. (2012) conducted a systematic literature review to describe PRO measures used to assess pain in trials of bisphosphonates for the treatment of bone metastases. As in our review, this study found that the BPI was the most commonly used multi-item instrument, while the most common approach for assessing pain was to administer a single-item scale such as the visual analogue scale, numerical rating scale, or verbal rating scale. The study also found that presentation of measures often lacked clear description, information on measurement properties, citations, clarity regarding method of administration, and consistent instrument names [53]. Clark et al. (2014) evaluated and compared PRO claims granted by FDA and EMA for five recently approved treatments in metastatic prostate cancer. Among the measures examined, this study recommended the Brief Pain Inventory-Short Form (BPI-SF) worst pain item for use in combination with analgesic use assessment to evaluate pain progression and pain palliation. Despite availability of a range of research in this area, there are still plenty of challenges in measurement of pain palliation in cancer clinical studies [54, 55]. In a recent FDA communication, Basch et al. (2013) highlighted that clinical studies should clearly document and use measures of pain intensity and analgesic use that are reliable, valid, and sensitive to changes over time and consistent with FDA patient-reported outcome guidance [55]. Future research

should examine the impact of SREs on pain in prostate cancer in the context of measurement properties of the PRO measures used.

Conclusions

Bone fracture and spinal cord compression have a profound negative impact on pain and QOL as well as on the morbidity of prostate cancer patients with bone metastases. Bone fracture and spinal cord compression are markers of advanced disease and may be found in patients with shortened survival. Radiation therapy and bone surgery, when used to treat fracture, spinal cord compression, and severe pain, generally improve clinical outcomes. Yet, up to 29 % of patients may experience progression in pain or no response to treatment, highlighting a need for more effective treatment of skeletal-related events in prostate cancer patients.

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