

SYSTEMATIC REVIEW OF SKELETAL-RELATED EVENTS IN PROSTATE CANCER

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Objectives

Between 65%-75% of patients with prostate cancer experience metastatic bone disease (Costa et al. 2008). Metastatic bone lesions increase risk for skeletal-related events (SREs), which according to the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) include clinical SREs (pathologic fracture, spinal cord compression, hypercalcemia of malignancy) and treatment of clinical SREs (radiotherapy or surgery to bone) resulting from severe bone pain.

Our objective was to systematically review the literature on the impact of SREs on pain, quality of life (QOL), morbidity, survival, and cost 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" for cancers of interest ("prostate cancer," "renal cancer," "multiple myeloma," "lung cancer," or "breast cancer"). Articles were included if they were randomized controlled trials, clinical

trials with a control group, systematic reviews, meta-analyses, case series, or economic analyses; 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 were identified under the "radiation therapy" key terms in our systematic search and were not excluded from our review. Articles on denosumab were not included in this review since they were published after our systematic search was completed.

Results

- A total of 209 articles were screened, of which 131 were excluded and 78 were abstracted.
- Forty-six of the 78 abstracted articles included prostate cancer patients.



The Impact of SREs on Pain

- A variety of scales were used.

Impact of Clinical SREs as a Group on Pain

- DePuy et al. (2007): patients with ≥ 1 SREs showed a larger increase in pain in the subsequent 360-day period as measured by the brief pain inventory.
- Weinfurt et al. (2005): presence of SREs reflected decrements in brief pain inventory scores.
- Saad et al. (2002): despite reduction in SREs, no difference in analgesic scores between treatment and placebo groups.

Impact of Clinical SREs on Pain

- We did not find any studies on the impact of pathologic bone fractures and hypercalcemia on pain.
- Aass et al. (2005) studied postradiation therapy for spinal cord compression; pain-free patients increased from 2% to 11%, and patients with pain "often and all the time" decreased from 50% to 15.6%.

Impact of Treatment of Clinical SREs on Pain

- Impact of radiation therapy (XRT) on pain, percent of patients with a pain relief response:

Impact of XRT on Pain	Proportion	References
Some pain relief	65%	Hird 2009; Weinfurt 2005
Partial/complete pain relief	45%-76%	Aass 2005; Berg 2009; Salazar 2001
Complete pain relief	1%-34%	Aass 2005; Hamouda 2007; Hartsell 2005; Hird 2009; Sze 2006

- Impact of bone surgery on pain, percent of patients with a pain relief response:

Impact of Bone Surgery on Pain	Proportion	References
Some pain relief	71%-72%	Ibrahim 2008; Liberman 2009
No pain relief	11%-24%	Ibrahim 2008; Liberman 2009
Worsening pain	4%-18%	Ibrahim 2008; Liberman 2009
Reduction in opioid use	67%	Liberman 2009
VAS score of "0"	50%	Liberman 2009

VAS = visual analogue scale.

Additional Considerations: Impact of Radionuclide Therapy on Pain

- Although radionuclide therapy (RNT) is not part of the FDA- or EMA-accepted definition of an SRE, it is a common treatment of SREs and impacts clinical outcomes of interest; thus, the 20 identified RNT articles were included in our review (e.g., Zafeirakis, 2010).
- Thirteen studies reported that RNT for SREs decreased pain in prostate cancer patients.

Impact of RNT on Pain	Proportion	No. of studies
Excellent/complete pain relief	15%-40%	6
Some pain relief	54.6%-80%	10
No pain relief	19%-45%	4
Stable/worsening pain	37.7%	1
Reduction in opioid use/analgesic scores		2
Reduction in VAS or BPI		6

BPI = brief pain inventory; VAS = visual analogue scale.

Impact of SREs on Quality of Life, Morbidity, Survival, and Cost

Five bisphosphonate trials examined the impact of SREs as a group:

- Patients with SREs had worse QOL, worse survival, and SREs increased cost.

Impact of SRE as a Group			
Quality of Life	Morbidity	Survival	Cost
<ul style="list-style-type: none">Significantly worse QOL on FACT-G (DePuy, 2007).Decrements in FACT-G and EuroQol but not stat. sig. (Weinfurt, 2005).No stat. sig. difference in FACT-G between Tx and placebo groups with reduction in SREs (Saad, 2002).	<ul style="list-style-type: none">Despite reduction in SREs, no stat. sig. difference in ECOG PS between Tx and placebo groups (Saad, 2002).	<ul style="list-style-type: none">Patients with no SREs had greater 1-year survival than patients with SREs (49.7% vs. 28.2%; $P=0.02$). (DePuy, 2007).	<ul style="list-style-type: none">6,973€ (Euros) per SRE in 24 months (Groot, 2003)\$12,469 in first year (Lage, 2008)\$12,300 to prevent 1 SRE with bisphosphonates during mean of 9 months (McKeage, 2008).

ECOG PS = Eastern Cooperative Oncology Group performance status; FACT-G = Fundamental Assessment of Cancer Therapy General Scale; Tx = treatment group.

Five studies examined individual clinical SREs:

- No data were found on the impact of hypercalcemia.
- Pathologic bone fractures decreased QOL, increased risk of death, and increased costs.

Impact of Malignant Bone Fracture			
Quality of Life	Morbidity	Survival	Cost
<ul style="list-style-type: none">Decline in physical and emotional well-being (FACT-G) and in EuroQol utility and VAS scores after pathologic fractures (Weinfurt, 2005).	No data	<ul style="list-style-type: none">Pathologic fractures associated with increased risk of death (Saad, 2007).	<ul style="list-style-type: none">Fracture increased care cost by \$14,061 (Krupski, 2007).

FACT-G = Fundamental Assessment of Cancer Therapy General Scale; VAS = visual analogue scale.

- Spinal cord compression decreased survival. Treatment reduced morbidity.

Impact of Metastatic Spinal Cord Compression (MSCC)			
Quality of Life	Morbidity	Survival	Cost
No data	<ul style="list-style-type: none">Improved Barthel score (Aass, 2005) and ECOG PS (Rades, 2006) with treatment of MSCC.	<ul style="list-style-type: none">Decreased survival in prostate cancer patients compared with similar patient cohorts (Rades, 2006; Aass, 2005).	No data

Barthel ADL questionnaire = Barthel activities of daily living questionnaire; ECOG PS = Eastern Cooperative Oncology Group performance status.

Twelve studies examined treatment of clinical SREs:

- Radiation therapy improved QOL.

Impact of Radiation Therapy			
Quality of Life	Morbidity	Survival	Cost
<ul style="list-style-type: none">Stat. sig. decline in 4 of 5 FACT-G scores and EuroQol utility and VAS scores after radiation (Weinfurt, 2005).No improvement in EORTC QLQ-C30 nausea and fatigue (Berg, 2009).Improvement in %NPR after HBI (Salazar, 2001).	No data	<ul style="list-style-type: none">Those who achieved complete pain relief had better survival than those who responded partially (Salazar, 2005).	No data

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; FACT-G = Fundamental Assessment of Cancer Therapy General Scale; HBI = half-body irradiation; VAS = visual analogue scale; %NPR = percent net pain relief.

- Bone surgery increased costs:

Impact of Bone Surgery			
Quality of Life	Morbidity	Survival	Cost
No data	No data	No data	<ul style="list-style-type: none">£18,000 (GBP) for orthopedic surgery (multiple cancer types) (Ashford, 2010).

Additional Considerations

- Malignant bone pain was a major determinant of QOL and was associated with shorter survival (multiple studies: e.g., Jønler, 2005).
- The overall impact of SREs would be even larger if RNT was included in the definition of SREs since RNT was found to decrease pain and morbidity and improve QOL.

Conclusions

- In conclusion, our literature review shows that clinical SREs are associated with worse clinical outcomes, including worsening of pain, QOL, morbidity, and survival.
- Our review also indicates treatment of clinical SREs is associated with decreased pain and improved QOL among prostate cancer patients, although there is still a need for more effective treatment of SREs.
- In addition, SREs appear to increase costs substantially.

- 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 XRT in the palliative treatment of metastatic bone lesions.
- Our review emphasizes that 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.

Key References

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