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Title

Assessing pharmacological interventions for bone metastases: the need for more patient-centred outcomes

Perspectives article

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Summary

Bone metastases are associated with a broad spectrum of clinical sequelae. Pain, reduced mobility, skeletal complications and treatment-related events reduce quality of life. Numerous randomised controlled trials have evaluated pharmacological interventions to treat bone metastases. The primary outcomes used have evolved over the past 25 years; from improvement in pain to time-to-first skeletal related event (SRE). An SRE consists of pathological fracture, spinal cord compression or need for radiotherapy or surgery to the bone. Currently used outcomes can detect small differences between interventions. However there are several limitations to SRE-related outcomes. In this article we illustrate the evolution of outcomes used in RCTs, critically appraising current outcomes used and proposing that more patient-centred outcomes are needed.

Key words

Bone metastases

Skeletal-related events

Bisphosphonates

Denosumab (Xgeva)

Time to event analysis

Multiple event analysis

Introduction

Bone is a common location for metastatic spread of cancer. Approximately 5% of women with breast cancer will develop bone metastases within five years of diagnosis (1). In lung cancer, it is estimated that 36% of patients have bone involvement at death (2). Bone metastases are considerably more common in prostate cancer. Bubendorf and colleagues (3), performed autopsies on over 1,500 men with prostate cancer and found that 90% had evidence of bone involvement. Any cancer has the potential to metastasise to bone, but the commonest causes of bone metastases are cancers of the breast, prostate, lung, bladder, thyroid and kidney.

Bone metastases are associated with reduced survival, increased complications and decreased quality of life (4,5). The clinical sequelae of bone metastases vary considerably. Pharmacological interventions are available to improve symptoms and reduce the risk of complications. Recent trials have used a composite outcome, known as skeletal related events (SRE) (6-11), which consists of pathological fracture, spinal cord compression, or need for radiation or surgery to the bone.

The outcomes chosen by trialists have wide ranging consequences; policy makers use this information to assist decision-making, future trial outcomes are designed in the context of previous research and the focus of treatment for clinicians and patients can be affected. In pharmacological trials of bone metastases, the SRE composite outcome has evolved over the past 25 years. In this article, we describe and explain the trend in outcomes used in pharmacological trials for bone metastases, critically appraising the current SRE outcome and propose that a more patient-centred outcome should be adopted.

Overview of pathophysiology

Metastatic disease within bone causes structural weakness by dysregulation of osteoblasts and osteoclasts. Pathophysiology of bone metastases has been illustrated by the “seed and soil” hypothesis (12). Bone marrow is an ideal “soil” because of the presence of an excellent reserve of micronutrients and growth factors. A good blood supply allows easy transportation of the “seed” (tumour cells).

Tumour cells interfere with the balance of osteoblasts and osteoclasts. Osteoblasts are responsible for bone formation, whereas osteoclasts resorb bone. Their synergistic action results in a constant turnover of bone and is dependent on a complex cascade of growth factors, cytokines, receptors and intracellular signals. There are a number of important mediators of bone resorption including dickkopf homolog 1 (Dkk1), stromal derived factor-1 alpha (SDF-1a), transforming growth factor beta (TGF-β), macrophage inflammatory protein-1a (MIP-1α), c-MET, SRC kinase and proteases including cathepsins and matrix metalloproteases. One such mediator is receptor activator of nuclear factor-κB ligand (RANKL), which induces osteoclast activity (and subsequent bone resorption) and is the target of the drug denosumab.

Pharmacological therapies may be more effective in a certain type of bone metastases . For example, zoledronic acid has been shown to be more effective than pamidronate in lytic bone metastases in breast cancer (13). The nature of bone metastases depends on the extent to which osteoclasts or osteoblasts are activated. An over-activity of osteoclasts results in mainly lytic (osteolytic) lesions, whereas over-activity of osteoblasts results in sclerotic (ostesclerotic or osteoblastic) lesions. Both sclerotic and lytic lesions cause disruption of the normal bone architecture resulting in structural weakness. Based on radiological appearance bone metastases can be categorised as sclerotic, lytic or mixed. Generally speaking, prostate cancer results in mainly sclerotic lesions and breast cancer lytic lesions (14). However, bone metastases should be considered in the context of a spectrum of lesions from lytic to sclerotic, with no lesion being purely lytic or sclerotic.

Spectrum of clinical sequelae associated with bone metastases

An understanding of the spectrum of the clinical sequelae associated with bone metastases is crucial when considering trial outcomes. The clinical sequelae associated with bone metastases are three-fold; 1) reduced survival, 2) increased risk of complications and 3) decreased quality of life. The sequelae are different for each patient, depending on location, type and number of bone metastases.

The main complications related to bone metastases are pathological fracture, hypercalcaemia, spinal cord compression and treatment-related events. Pathological fractures are caused by increased bone fragility due to sclerotic or lytic lesions. Fractures of the long bones or axial skeleton are commonest. Pathological fractures can range from asymptomatic fractures incidentally identified on radiological investigation, to disabling long bone fractures causing immobility.

Spinal cord compression (SCC) is the most serious complication. It can be caused by an impinging fracture or direct tumour growth. Paraplegia can ensue if SCC is not diagnosed at a sufficiently early stage or if the compression is not amenable to treatment. As with pathological fracture, there is a breadth of possible clinical outcomes, from mild sensory loss to complete paraplegia. Hypercalcaemia is caused by release of calcium from bone metastases and dysregulation of normal calcium homoeostasis.

There is a clear association between reduced survival and bone metastases. In prostate cancer, five year survival drops from 56% to 3% with the presence of bone metastases (4). Breast cancer with associated bone metastases is associated with a five year survival of 20% (5). However reduced survival with bone metastases mainly reflects disease progression, rather than mortality directly caused by bone metastases. For example, in breast cancer median survival is estimated to be 2.1 years for patients with bone metastases only, compared with 1.6 years for patients with bone and visceral metastases (15). Bone metastases can cause mortality by complications, such as hypercalcaemia, spinal cord compression or pathological fractures. Saad and colleagues (16) found that pathological fractures were associated with reduced survival, an association which has been supported by other studies (4,5). Whether or not the reduced survival is caused by a pathological fracture or a confounder, such as disease progression, is not clear.

Quality of life is decreased by a convergence of increased pain, reduced mobility and incidence of complications. Pain associated with bone metastases is often severe and can be difficult to control with analgesia. Mobility is reduced by asthenia, bone pain, pathological fractures, nerve root compression or spinal cord compression. Subsequently quality of life decrement can vary dramatically between patients.

Current treatment options

Current treatment for bone metastases includes supportive care with or without bone targeting drugs as well as treatment of the underlying systemic malignancy. Supportive care consists of therapies tailored to each individual patient, eg, analgesics, radiotherapy or surgery to bone to treat or prevent fractures. There are currently two main classes of bone metabolism targeted drugs used in the treatment of malignant bone disease; bisphosphonates and a RANKL-targeted antibody, denosumab.

Bisphosphonates inhibit osteoclasts, reducing bone resorption. There are currently four bisphosphonates licensed for treatment of bone metastases – zoledronic acid (all advanced malignancies), disodium pamidronate (breast cancer or multiple myeloma), ibandronic acid (breast cancer only) and sodium clodronate (breast cancer or multiple myeloma). Current National Institute for Health and Clinical Excellence (NICE) guidelines recommend that all patients with symptomatic bone metastases secondary to breast or castration resistant prostate cancer for whom conventional treatments have failed should be considered for treatment with bisphosphonates (Clinical Guideline 81 (101) and Clinical Guideline 58 (102)). Published guidelines by the American Society of Clinical Oncology recommend the use of bisphosphonate for all patients with bone metastases secondary to breast cancer (17).

Denosumab is a fully human monoclonal antibody that inhibits RANKL. It has been evaluated through three pivotal trials (9-11) and recently licensed by the European Medicines Agency for the prevention of skeletal related events in bone metastases from solid tumours (103). Denosumab has also been studied for the prevention of bone metastases (Smith 11).

New pharmacological interventions, such as SRC kinase inhibitors (18) and c-MET inhibitors (19), have been tested in early phase clinical studies and will soon be evaluated in phase 3 trials.

What outcomes have been used and are currently used?

Assessment of pharmacological interventions is challenging because of the spectrum of clinical sequelae from bone metastases. A number of different outcome measures have

been used in clinical trials over the past 25 years (20-51). Table 1 shows the evolution and trend of primary and secondary outcomes.

Very early trials (20, 22, 23) only included patients with bone pain at baseline and subsequently assessed improvement of pain. The majority of these trials were performed in prostate cancer, where metastatic bone pain can often be severe despite strong analgesics. In the 1990s, some trials started using skeletal events, such as pathological fracture or need for radiotherapy as primary outcomes (25, 35), but not as the SRE composite outcome. Quality of life measures and biochemical markers were also increasingly used during this period.

In 2000 Lipton and colleagues (36), reported the results of two randomised controlled trials (52, 53). The primary outcome in these trials was skeletal morbidity rate (SMR), defined as "the ratio of the number of skeletal complications experienced by a patient divided by the time on the trial for that patient (expressed as the number of events/year)". Skeletal complications were a composite endpoint and included pathological fracture, need for radiotherapy or surgery, spinal cord compression or hypercalcaemia. These skeletal complications would soon become known under the term skeletal-related events (SREs). Within the composite endpoint of SREs, some trials would include hypercalcaemia and/or change in anti-neoplastic medication. In recent trials, patients are screened radiologically for SREs on a regular basis, with both new asymptomatic and symptomatic fractures being included (9-11). Including asymptomatic events may overestimate treatment effects. However, some may argue that including asymptomatic fracture is appropriate, since it is likely that these fractures will become symptomatic. The relationship between such 'events' and actual morbidity remains far from clear.

Some authors argued that the proportion of patients requiring radiotherapy is the most appropriate outcome, since radiotherapy is the commonest SRE and repeated need for treatment would reduce quality of life (compared with pathological fractures which may be asymptomatic and not impact quality of life) (37). On the other hand, radiotherapy is accessible to most patients and can be highly effective in controlling bone pain with minimal toxicity, thus minimising the actual impact of the 'event' on quality of life.

Two trials evaluating ibandronic acid used an evolution of SMR, the skeletal morbidity period rate (SMPR) (42,43). The SMPR was introduced to overcome criticisms that SREs are often related to previous SREs. For example, a patient who suffers a pathological fracture may subsequently have surgery. This would be classified as two SREs. SMPR defines a period as 12 weeks. The trial lasted for 96 weeks, therefore patients who completed the trial would undergo eight 12-week periods. For each patient, the number of periods with a new SRE was calculated and divided by the total number of 12-week periods on study. However this does not allow for difference in time on-study. For example, a patient who leaves the trial after 12 week without an SRE is given the same score as a patient who finished the trial after 96 weeks without an SRE. To overcome this, authors used a 'revised rate ratio' using the calculation:

$$SMPR = \frac{number\ of\ periods\ with\ a\ new\ SRE + 1}{number\ of\ 12\ week\ periods\ on\ study + 0.5}$$

Therefore, the more 12 week periods a patient accumulates without an SRE the lower the SMPR will be. The aim is to prevent overestimation of the treatment effect. However the SMPR could have the opposite effect and underestimate effectiveness, if several independent SREs occurred within one period.

Three pivotal trials evaluating zoledronic acid, compared with pamidronate or placebo, addressed the criticism of dependent SREs by introducing a 21 day window (6-8); after a SRE occurs, no further SREs are counted for 21 days.

The primary outcome in the zoledronic acid trials (6-8) was the proportion of patients with at least one on-study SRE (including a 21 day window), but the trials also introduced two more outcomes; time-to-first SRE and time-to-first and subsequent SRE. These outcomes identify differences in delay of events (first and subsequent), even if the total number of events in each group are equal.

Time-to-first and subsequent SRE uses multiple event analysis (MEA). This method, first described by Andersen and Gill (54), includes a measure of both time and number of events.

It has been criticised because it does not differentiate between participants who have died and those who have left the trial (55). Other methods which incorporate mortality have been proposed (56, 57), but the Andersen-Gill method remains the most widely used.

The most recent trials, comparing denosumab with zoledronic acid, have used time-to-first SRE as the primary endpoint (9-11). Time-to-first and subsequent SRE is included as a secondary outcome.

Expert Commentary

What are the important outcomes for patients with bone metastases?

Trials should primarily assess the outcomes that are most important to patients and subsequently outcomes most important to the health and social services. Patients should be able to understand the outcome and evaluate the potential benefits that treatment may bring to them.

There are four main outcomes that are important to patients with bone metastases; 1) overall survival 2) quality of life 3) serious complications (such as spinal cord compression or long bone pathological fracture) and 4) treatment administration and adverse events. Quality of life measures encompass a number of different events and symptoms, such as pain and reduced mobility.

Since health and social care is delivered in an environment of limited resources with opportunity costs, relevant outcomes relate to resource use, such as management of disease progression and complications, administration of treatments and provision of care.

What are the strengths and limitations of the current outcomes?

SRE composite outcome

The composite SRE outcome allows for increased power and efficiency. To detect clinically meaningful differences in each event (such as spinal cord compression), large study numbers would be needed. Furthermore, it could be argued that one composite outcome is easier for clinicians, patients and researchers, opposed to several individual outcomes.

However there are significant limitations of the SRE composite outcome. The SRE composite outcome includes a wide spectrum of outcomes and is therefore of little use to patients. An asymptomatic fracture and spinal cord compression leading to paraplegia are given equal weight. For example, in the study performed by Saad and colleagues (6), zoledronic acid reduced the absolute risk of experiencing an on-study SRE by 11% (95% CI 1.8% to 20.3%) compared to placebo. The obvious question from a patient's perspective is, do I have an 11% risk reduction of an asymptomatic event (asymptomatic fractures and change in anti-neoplastic medications were included) or a serious complication (spinal cord compression)? The answer is the patient has an 11% absolute risk reduction of experiencing any SREs, but a 9% (95%CI 1.8% to 16.3%) absolute risk reduction of experiencing a pathological fracture and 2.5% (95%CI -1.8 to 6.9) absolute risk reduction in spinal cord compression. In fact, when the SRE outcomes are divided in this study, only pathological fractures show a significant difference. The trial included approximately 205 patients in each arm and would require substantially more to be sufficiently powered to detect differences in individual SREs.

The SRE outcome is further complicated by including both treatments (need for surgery or radiotherapy) and complications (pathological fracture and spinal cord compression).

Moreover the SRE outcome does not directly measure bone pain or mobility. Although need for radiotherapy is an indirect measure of bone pain, it would not be considered specific. Some patients may have generalised widespread pain that is not suitable for radiotherapy.

The SRE composite outcome can be subject to over-estimation. Frequent radiological screening of patients for SREs will identify more pathological fractures earlier. A study by Trinkaus and colleagues (58) compared the SRE frequency in patients treated with intravenous bisphosphonates in a "real life" setting, with the trial setting. The authors found a considerably lower incidence of SREs in the "real life" setting.

SRE incidence versus time to event analysis

The trial analysis methodology has evolved over the past 25 years to detect smaller differences. Time to first and time to first-and-subsequent analyses will detect very small differences between treatments. The need to detect small differences may be warranted, as new interventions are compared with active comparators. Statistically significant differences may be demonstrated, but it is important to ensure that these are clinically meaningful.

Time to event analyses and multiple event analyses reflect a delay, not prevention, of complications. Time-to-first SRE is a relatively simple measure. However multiple event analysis adds an additional layer of complexity that may prove difficult for patients and their physicians to understand. In addition, multiple event analyses are more likely to show small differences between treatments that may not be clinically meaningful.

Five year view

What would be the ideal outcome?

The key question is, does a reduction in risk of SREs (measure with SRE incidence or time to event analysis) directly correlate with a reduction in decreased quality of life? If SRE events do not correlate with quality of life the validity of the SRE outcome is questionable. A disease specific quality of life measure should be sensitive to changes in bone pain, complications, mobility and treatment toxicity. Unfortunately detailed quality of life and pain outcomes have not been published to allow this sort of analysis. Some pain and quality of life outcomes have been published in abstract form (59-65), but generally continuous outcomes have been converted into categorical data and only selective subgroups reported.

The outcomes chosen by trialists are of paramount importance to patients, clinicians, researchers and the clinical pharmacology community. Outcomes affect the interpretation of effectiveness of the interventions, design of future trials, licensing indications and possibly the attention of clinicians. Table 1 illustrates how outcomes chosen by trialists affect future trials. The term SRE has appeared in licensing indications. The European

Medicines Agency has licensed denosumab for the “prevention of skeletal related events in bone metastases from solid tumours” (103). The primary goal of clinicians and the pharmacology community should be to improve the quantity and quality of life for patients with bone metastases. Trials that focus on preventing SREs may divert the attention of clinicians from this goal.

An analysis correlating SRE outcome and quality of life or pain scores is needed. Both generic (e.g. EQ5D) and disease specific (e.g. FACT) quality of life measures should be used. However this will only be possible if detailed quality of life data are published. Alternatively a mixed-method study measuring qualitative data alongside a RCT could be designed to evaluate the impact of individual SREs on patients.

We propose that trialists move more towards patient-relevant outcomes. Primary outcomes should include patient-centred outcomes such as direct measures of pain and mobility. A robust composite endpoint which accurately reflects the benefits of a new treatment is unlikely to be found. Disease specific quality of life measures may be the closest trialists will get to a composite endpoint that encapsulates all benefits. Alternatively several individual outcomes could be reported, such as pain scores, mobility indices, incidence of fractures/spinal cord compression/hypercalcaemia, but this is unlikely to be acceptable for the purposes of drug registration. In the meantime we recommend that the SRE outcome should be reported alongside quality of life scores and be interpreted with caution.

Key issues

- Bone metastases are associated with a spectrum of clinical sequelae
- Numerous randomised controlled trials have evaluated pharmacological interventions
- Early trials measured improvement of bone pain, most recent trials assess time-to-first skeletal-related event (SRE)
- The composite SRE endpoint consists of pathological fracture, spinal cord compression or need for radiotherapy or surgery to bone, with each component given equal weight
- The SRE endpoint is of little use to patients since it encompasses a wide spectrum of clinical events
- It is unclear if improvement in SRE outcomes directly correlate with improvements in quality of life
- An endpoint that reflects the most important outcomes to patients is needed
- It is unlikely that a robust composite outcome will be found
- Disease specific quality of life measures may be the closest trialists get to an outcome that encompasses as many treatment benefits as possible.

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Table 1: Primary and secondary outcomes

First author and year	Primary tumour	Intervention	Comparison	Primary outcome	Secondary outcomes
Buchali 1988 (20)	Prostate	Strontium (iv)	Placebo	Improvement in bone pain (subjective reporting)	Overall survival Effects on blood cell count
Elomaa 1988 (21)	Breast	Clodronate (oral)	Placebo	Biochemical markers	Survival
Adami 1989 (22)	Prostate	Clodronate (iv+im+oral)	Placebo	Improvement in bone pain (analgesic use and VAS)	Haematological toxicity
Smith 1989 (23)	Prostate	Etidronate (iv+oral)	Placebo	Improvement in bone pain (analgesic use and VAS)	
Elomaa 1992 (24)	Prostate	Clodronate (iv)	Placebo	Improvement in bone pain (subjective and analgesic use)	Survival Serum calcium
Paterson 1993 (25)	Breast	Clodronate (oral)	Placebo	Incidence of HCM, fracture and need for radiotherapy	Cumulative skeletal morbidity Survival Bone pain
Kylmala 1993 (26)	Prostate	Clodronate (iv)	Open	Improvement in bone pain (subjective and analgesic use)	Bone markers Radiological appearance Biochemical markers Survival
Porter 1993 (27)	Prostate	Strontium (iv)	Placebo	Delay and improvement of pain (scores and analgesic use)	Survival Need for radiotherapy Quality of life Biochemical markers
Quilty 1994 (28)	Prostate	Strontium (iv)	Radiotherapy	Improvement in bone pain (subjective and analgesic use)	Performance status Survival
Robertson 1995 (29)	OST	Clodronate (oral)	Placebo	Improvement in bone pain (analgesic use and VAS)	Survival
O'Rouke 1995 (30)	OST	Clodronate (oral)	Placebo	Biochemical markers	Improvement in bone pain
Kylmala 1997 (31)	Prostate	Clodronate (iv+oral)	Placebo	Improvement in bone pain (WHO classification)	Performance status Biochemical markers Radiological progression
Strang 1997 (32)	Prostate	Clodronate (iv)	Placebo	Improvement in bone pain (analgesic use and VAS)	
Piga 1998 (33)	OST	Clodronate (oral)	Placebo	Performance status	Improvement in bone pain (analgesic use and VAS)
Arican 1999 (34)	Prostate	Clodronate (oral)	Placebo	Improvement in bone pain (analgesic use and VAS)	Performance status Bone markers
Kristensen 1999 (35)	Breast	Clodronate (oral)	Open	Incidence of HCM, fracture or need for radiotherapy	Bone markers Pain

					Quality of life (HADs and EORTC-QLQ)
Lipton 2000 (36)	Breast	Pamidronate (iv)	Placebo	SMR*	Incidence of SRE* Pain Quality of life (Spitzer index) Performance status Bone markers
Berenson 2001 (37)	OST	Zoledronic acid	Pamidronate (iv)	Proportion of patients requiring radiotherapy	Incidence of SREs* Bone mineral density Performance status Bone pain
Jagdev 2001 (38)	OST	Clodronate (oral)	Pamidronate (iv)	Improvement in pain (subjective response)	Biochemical markers
Saad 2002 (6)	Prostate	Zoledronic acid	Placebo	Proportion of patients with ≥1 SRE†	Time to first SRE† SMR† Time to disease progression Bone markers Quality of life
Small 2003 (39)	Prostate	Pamidronate (iv)	Placebo	Improvement in bone pain (analgesic use and BPI)	Proportion with SRE* SMR Mobility (walking speed) Tumour markers
Ernst 2003 (40)	Prostate	Clodronate (iv)	Placebo	Improvement in bone pain (palliative response criteria (moore 94 JCO)	Quality of life Symptomatic progression PSA response Incidence of HCM, radiotherapy and pathological fractures
Dearnaley 2003 (41)	Prostate	Clodronate (oral)	Placebo	Symptomatic bone progression free survival	Survival Biochemical markers Bone pain
Body 2003 (42)	Breast	Ibandronate (iv)	Placebo	SMPR**	Bone pain Performance status Survival Bone markers
Rosen 2003a (7)	Breast	Zoledronic acid	Pamidronate (iv)	Proportion of patients with ≥1 SRE	Time to first SRE Time to each SRE SMR MEA Survival Performance status
Rosen 2003b	OST	Zoledronic acid	Placebo	Proportion of patients with ≥1 SRE	Time to first SRE

(8)					SMR MEA Time to bone progression Survival Bone markers Bone pain
Body 2004 (43)	Breast	Ibandronate (oral)	Placebo	Skeletal morbidity period rate**	Bone pain Quality of life (EORTC-QLQ)
Kohno 2005 (44)	Breast	Zoledronic acid	Placebo	Ratio of SRE rate	Proportion of patients with ≥1 SRE* Time to first SRE* Multiple event analysis* Bone pain (BPI)
Nilsson 2005 (45)	Prostate	Strontium (iv)	FEM	Improvement in bone pain (analgesic use and VAS)	Performance status
Brown 2007 (46)	OST	Clodronate (oral)	Placebo	Bone markers	Bone pain (VAS)
Heras 2007 (47)	Colorectal	Ibandronate (iv)	Placebo	Proportion of patients with ≥1 SRE†	Time to first SRE† SMR† Time to progression of bone lesions Bone markers
Mystakidou 2008 (48)	OST	Ibandronate (oral)	Ibandronate (iv)	Clinical response based on radiographic appearance of lesions	Bone pain (BPI) Quality of life (FACT-G)
Heras 2009 (49)	Breast	Ibandronate (iv)	Placebo	Proportion of patients with ≥1 SRE†	Time to first SRE† MEA†
Zaghloul 2010 (50)	OST	Zoledronic acid	Placebo	Proportion of patients with ≥1 SRE*	Time to first SRE* Pain score Overall survival
Zhao 2011 (51)	OST	Zoledronic acid	Open	Bone markers	Survival Incidence of SREs*
Stopeck 2010 (10)	Breast	Denosumab	Zoledronic acid	Time to first SRE (non-inferiority)	Time to first SRE (superiority) MEA Overall survival Bone markers
Fizazi 2011 (11)	Prostate	Denosumab	Zoledronic acid		
Henry 2011 (9)	OST	Denosumab	Zoledronic acid		

OST = other solid tumours, iv = intravenous, im = intra-muscular, FEM = 5-FU, epirubicin and mitomycin, VAS = visual analogue scale, EPRTC-QLQ = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, SRE = skeletal related event, MEA = multiple event analysis, BPI = brief pain inventory, VAS – visual analogue scale, SMR = skeletal morbidity rate

* includes hypercalcaemia ** revised event ratio method, † = includes change in anti-neoplastic therapy,