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[Intervention Review]

Pharmacological interventions for the prevention of insufficiency fractures and avascular necrosis associated with pelvic radiotherapy in adults

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ABSTRACT

Background

Pelvic radiotherapy is a treatment delivered to an estimated 150,000 to 300,000 people annually across high-income countries. Fractures due to normal stresses on weakened bone due to radiotherapy are termed insufficiency fractures. Pelvic radiotherapy-related interruption of the blood supply to the hip is termed avascular necrosis and is another recognised complication. The reported incidences of insufficiency fractures are 2.7% to 89% and risk of developing avascular necrosis is 0.5%. These complications lead to significant morbidity in terms of pain, immobility and consequently risk of infections, pressure sores and mortality.

Objectives

To assess the effects of pharmacological interventions for preventing insufficiency fractures and avascular necrosis in adults over 18 years of age undergoing pelvic radiotherapy.

Search methods

We performed electronic literature searches in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and DARE to 19 April 2017. We also searched trial registries. Further relevant studies were identified through handsearching of citation lists of included studies.

Selection criteria

Randomised controlled trials (RCTs) or non RCTs with concurrent comparison groups including quasi-RCTs, cluster RCTs, prospective cohort studies and case series of 30 or more participants were screened. We included studies assessing the effect of pharmacological interventions in adults over 18 years of age undergoing radical pelvic radiotherapy as part of anticancer treatment for a primary pelvic malignancy. We excluded studies involving radiotherapy for bone metastases. We assessed use of pharmacological interventions at any stage before or during pelvic radiotherapy. Interventions included calcium or vitamin D (or both) supplementation, bisphosphonates, selective oestrogen receptor modulators, hormone replacement therapy (oestrogen or testosterone), denosumab and calcitonin.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. We contacted study authors to obtain missing data. Data were to be pooled using the random-effects model if study comparisons were similar, otherwise results were to be reported narratively.

Main results

We included two RCTs (1167 participants). The first RCT compared zoledronic acid with placebo in 96 men undergoing pelvic radiotherapy for non-metastatic prostate cancer.

The second RCT had four treatment arms, two of which evaluated zoledronic acid plus adjuvant androgen suppression compared with androgen suppression only in 1071 men undergoing pelvic radiotherapy for non-metastatic prostate cancer.

Both studies were at a moderate to high risk of bias and all evidence was judged to be of very low certainty.

The studies provided no evidence on the primary outcomes of the review and provided limited data in relation to secondary outcomes, such that meta-analyses were not possible. Both studies focused on interventions to improve bone health in relation to androgen deprivation rather than radiation-related insufficiency fractures and avascular necrosis. Few fractures were described in each study and those described were not specific to insufficiency fractures secondary to radiotherapy. Both studies reported that zoledronic acid in addition to androgen deprivation and pelvic radiotherapy led to improvements in BMD; however, the changes in BMD were measured and reported differently. There was no available evidence regarding adverse effects.

Authors' conclusions

The evidence relating to interventions to prevent insufficiency fractures and avascular necrosis associated with pelvic radiotherapy in adults is of very low certainty. This review highlights the need for prospective clinical trials using interventions prior to and during radiotherapy to prevent radiation-related bone morbidity, insufficiency fractures and avascular necrosis. Future trials could involve prospective assessment of bone health including BMD and bone turnover markers prior to pelvic radiotherapy. The interventions for investigation could begin as radiotherapy commences and remain ongoing for 12 to 24 months. Bone turnover markers and BMD could be used as surrogate markers for bone health in addition to radiographic imaging to report on presence of insufficiency fractures and development of avascular necrosis. Clinical assessments and patient reported outcomes would help to identify any associated adverse effects of treatment and quality of life outcomes.

PLAIN LANGUAGE SUMMARY

Do medicinal interventions reduce radiation-related bone fractures and risk of avascular necrosis in adults undergoing pelvic radiotherapy?

What is the issue?

Research shows that pelvic radiotherapy can cause changes in pelvic bones, which may lead to fractures occurring from minimal trauma (called insufficiency fractures) and permanent damage to bone from interrupted blood supply (called avascular necrosis). These conditions can result in pain, problems with mobility, hospitalisation, need for surgery and death. This review looked at the literature for medicines which may be given prior to or during pelvic radiotherapy, to determine if these could reduce the incidence of insufficiency fractures and avascular necrosis, and improve bone health and quality of life.

How did we conduct the review?

We searched the medical literature up to April 2017 for studies of interventions aimed at preventing fractures and avascular necrosis in people undergoing radiotherapy as part of cancer treatment, with the intention of pooling data from different studies if the study comparisons were similar.

What evidence did we find?

We found two studies where people were randomly put into one of two or more treatment groups (called randomised controlled trials) which were sufficiently relevant to the review topic. Both studies, which involved 1167 participants altogether, were conducted in men undergoing radiotherapy for prostate cancer and evaluated a bisphosphonate medicine called zoledronic acid. These men also received hormone treatment for their condition as reduced bone mineral density (BMD; how many minerals are in the bones, which determines how solid and strong the bones are) is a known side effect of this treatment. Studies measured and reported outcomes differently and we were unable to pool their results (data); however, limited evidence suggested that zoledronic acid might improve BMD in this specific group (men with prostate cancer) who received both hormone treatment and radiotherapy. There were few fractures or avascular necrosis events in the studies, therefore, it is very uncertain whether zoledronic acid has an impact on these important outcomes. As the studies were not specifically designed to evaluate the effect of zoledronic acid on radiotherapy-related bone outcomes, and participants also received hormone treatment, it is very uncertain whether the evidence applies to people undergoing pelvic radiotherapy for other cancers and people not receiving adjuvant hormone treatment.

Both studies were at a moderate to high risk of bias and all evidence was judged to be of very low certainty.

What does this mean?

There is insufficient evidence that zoledronic acid and other medicines prevent radiotherapy-induced bone complications. This review highlights the need for clinical trials using interventions prior to and during radiotherapy to prevent radiation-related bone morbidity, insufficiency fractures and avascular necrosis.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Pharmacological intervention compared with no intervention for prevention of radiation-related insufficiency fractures and avascular necrosis

Pharmacological intervention compared with no intervention for prevention of radiation-related insufficiency fractures and avascular necrosis

Patient or population: Adults undergoing pelvic radiotherapy

Settings: Intervention prior or during radiotherapy; hospital

Intervention: Zoledronic acid

Comparison: No intervention

Outcomes	No of participants (studies)	Quality of the evidence (GRADE)	Comments
<p>The 2 included studies did not fully describe the radiotherapy techniques used.</p> <p>The dose, delivery of treatment (conformal, intensity modulated, brachytherapy) and, therefore, volume of pelvis irradiated could influence the pattern of bone fractures, changes in BMD and risk of avascular necrosis.</p> <p>Studies were heterogeneous in other aspects so meta-analyses were not performed and results were reported as a narrative.</p>			
Insufficiency fractures and avascular necrosis	<p>Kachnic 2013 (96 eligible participants)</p> <p>Out of the 91 men (95% of eligible participants) who consented to QoL data collection, participant compliance for completing the FACT-G was 96% at baseline, 82% at 12 months, 71% at 24 months and 58% at 36 months.</p>	<p>⊕⊕⊕⊕ Very low^{1,2}</p>	<ul style="list-style-type: none"> • Kachnic 2013 reported 1 fracture occurring in each intervention group. • Denham 2014 reported 72 non-spinal fractures (38 in intervention group). Only 3 fractures were near the radiation field and 1 case of avascular necrosis but details of the intervention group for these was not provided. • Data were sparse, and the imaging and investigations used did not meet the review criteria.
BMD and fracture risk	<p>Denham 2014 (905 participants had thoracolumbar x-rays available for assessment out of a possible 1167)</p> <p>(222 participants for BMD sub study).</p>	<p>⊕⊕⊕⊕ Very low^{1,2}</p>	<ul style="list-style-type: none"> • Improvements in BMD in both studies. • 1 RCT reported significant percentage increases in BMD at 36 months in the lumbar spine (6% with zoledronic acid versus -5% with control; $P < 0.0001$), left hip (1% with zoledronic acid versus -8% with control; $P = 0.0002$) and left femoral neck (3 with zoledronic acid versus -8% with control; $P = 0.0002$) (Kachnic 2013). • In comparison, the other RCT had a sub study assessing the change in mean total hip BMD at 24 and 48 months (Denham 2014). For the 6-month androgen deprivation group, there was no change in BMD at 24 months (0.6%; $P = 0.18$) but a significant increase at 48 months (1.8%; $P = 0.003$). In the 12-month androgen deprivation group, there was no significant change in BMD at 24 months (0.5%; $P = 0.41$) and a tendency towards significance at 48 months (1.2%; $P = 0.09$). • As different time points and sites were used to measure changes in BMD, a further analysis was difficult to perform. • Only 1 RCT reported fracture risk, but the risk was assessed using a non-validated method, so further analysis was not conducted (Denham 2014).

Bone turnover markers	⊕⊕⊕⊕ Very low ^{1,2}	<ul style="list-style-type: none"> The 2 included RCTs did not report changes in bone turnover markers between control and intervention groups, preventing further reporting on these outcomes.
QoL	⊕⊕⊕⊕ Very low ^{1,2,3}	<ul style="list-style-type: none"> Only 1 RCT reported QoL and suggested there were no differences in QoL between groups (Kachnic 2013). However, this study only accrued small patient numbers and only 58% QoL data were obtained at 36 months so there was likely to be a lack of statistical power to detect any true differences. Neither trial reported bone symptoms or unplanned hospital stays.
Mortality	⊕⊕⊕⊕ Very low ^{1,2,4}	<ul style="list-style-type: none"> Neither trial reported cancer-specific mortality of overall mortality.
Adverse events	⊕⊕⊕⊕ Very low ^{1,2}	<ul style="list-style-type: none"> Both included RCTs did not fully describe the radiotherapy techniques used. The dose, delivery of treatment (conformal, intensity modulated, brachytherapy) and, therefore, volume of pelvis irradiated could influence the pattern of bone fractures, changes in BMD and risk of avascular necrosis. 1 RCT had an imbalance in the sub study groups reporting on changes in BMD, where 1 group may have had higher risk factors for osteoporosis that could bias the results (Denham 2014). The results reported by Kachnic 2013 need to be interpreted with caution as the study had inadequate accrual, therefore, lacked statistical power to detect differences. Adverse events and compliance to the intervention reported descriptively.

BMD: bone mineral density; FACT-G: Functional Assessment of Cancer Therapy - General; QoL: quality of life; RCT: randomised controlled trial.

[GRADE Working Group](#) grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹Downgraded as both studies had a low reported number of fractures but the details of the fracture (location, nature) were not described and hence there was uncertainty regarding these being insufficiency fractures from radiotherapy.

²Quality of evidence downgraded due to heterogeneity, poor reporting of results and limitations in study methodology (risk of bias).

³Downgraded as QoL not reported in the large trial ([Denham 2014](#)).

⁴Downgraded as neither trial reported other potentially important outcomes such as survival, bone symptoms and unplanned hospital stay.

BACKGROUND

Description of the condition

Radiotherapy-related bone disease is increasingly recognised as an important, yet under-researched area. In the UK, 17,000 people per year are treated with pelvic radiotherapy (West 2009) for gynaecological, colorectal, prostate and bladder cancers. It is estimated that 150,000 to 300,000 people across high-income countries are treated annually (Andreyev 2005; Hauer-Jensen 2003).

An insufficiency fracture is a type of stress fracture that can occur during or after radiotherapy in the presence of minimal or no trauma. Pelvic radiotherapy can cause microvascular occlusion (blockage of small blood vessels) in bone, which results in bone necrosis (cell death) and altered osteoblastic function (osteoblasts are bone-forming cells) and eventually bone fragility (Hopewell 2003). Reported bone abnormalities after pelvic radiotherapy include bone marrow signal changes, insufficiency fractures (Baxter 2005), and femoral head avascular necrosis (necrosis due to interrupted blood supply to the femur bone which forms the main hip joint). Reported incidences of insufficiency fracture after pelvic radiotherapy range between 2.7% and 89% (Bliss 1996; Blomlie 1996), with femoral head avascular necrosis occurring in up to 0.5% to 1% (Bliss 1996; Kwon 2008); these fractures have been noted in people receiving pelvic radiotherapy for gynaecological (endometrial/cervical) cancers (Ikushima 2006; Shih 2013), and prostate (İğdem 2010), anal and rectal cancers (Dzik-Jurasz 2001; Herman 2009; Kim 2012). The timing of development of fractures is variable; reports in the literature describe fractures diagnosed between two and 63 months after completion of radiotherapy, with reported median time to development of six to 20 months (Erickson 2000; Ikushima 2006; Kwon 2008; Schmeler 2010). Approximately 43% to 77% of people are symptomatic (Abe 1992; Kwon 2008) and experience pain that can impact their quality of life (QoL), resulting in long-term morbidity.

Once an insufficiency fracture has been identified, treatment is generally conservative and includes analgesia and rehabilitation. Resolution of symptoms can take between one and 35 months, and a minority of people remain persistently symptomatic (Blomlie 1996; Huh 2002; Ikushima 2006; Ogino 2003).

Few data are available regarding mortality rates due to pelvic insufficiency fractures associated with pelvic radiotherapy. However, mortality rates of 14% and 23% for pelvic insufficiency fractures in general have been reported at one year in older people (Mears 2011; Taillandier 2003). It has been well documented that mortality is significantly increased during the first year after a hip fracture (Baxter 2005). Evidence suggests that increased mortality risk can persist for some years (Bliuc 2009), and that rates of mortality associated with insufficiency fractures and displaced pelvic fractures are similar in older people (Mears 2011).

Chemotherapy may be used alongside pelvic radiotherapy as curative treatment and is known to increase radiation toxicity, possibly including bone toxicity (Jenkins 1995; Kim 2012; Kirwan 2003). Steroids are associated with osteoporosis and increased risk of fracture (Bauer 2000; Ono 1992). Chemotherapy regimens often include co administered steroids, which may contribute to the associated increase in insufficiency fractures and osteonecrosis

(death of bone cells due to interrupted blood supply) although not all studies demonstrate this (Bauer 2000).

Risk factors such as osteoporosis (Kim 2012), older age (Park 2011; Schmeler 2010), low bodyweight (Oh 2008; Tokumaru 2012), and postmenopausal status (Abe 1992; Ikushima 2006) have also been associated with increased risk of insufficiency fracture after pelvic radiotherapy. Higher radiation dose, completion of treatment and use of concurrent chemotherapy all increase the chances of cancer cure; however, these factors are also associated with an increased incidence of toxicity, including risk of insufficiency fractures (Oh 2008).

Description of the intervention

Potential pharmacological interventions to prevent pelvic radiotherapy-induced insufficiency fractures are based on standard treatments for optimising bone health. There are various pharmacological agents that could be used to improve bone health in these people including:

- calcium and vitamin D combination/vitamin D monotherapy to promote adequate bone mineralisation;
- bisphosphonate drugs, which reduce bone resorption (breaking down of bone) by impairing the function of bone-resorbing cells, called osteoclasts;
- hormone manipulation using oestrogen and testosterone preparations and selective oestrogen receptor modulators (drugs that reduce bone resorption by binding to the oestrogen receptor in women);
- denosumab, an antibody drug that reduces the formation, function and survival of osteoclasts;
- teriparatide, a medication that promotes bone formation;
- calcitonin and strontium, drugs that affect bone resorption and formation, and are used in treatment for osteoporosis.

These interventions could potentially be employed before or during radiotherapy with the goal of preventing insufficiency fractures. They may be required for a defined period after radiotherapy, potentially up to 24 months, covering the time period over which most fractures are observed (Erickson 2000; Ikushima 2006).

Interventions used to improve bone health can be associated with adverse effects, which are commonly mild to moderate such as gastrointestinal upset. Some interventions can have serious adverse effects, such as bisphosphonates and denosumab, which may cause low calcium levels and rarely, ulceration and breakdown of the jaw bone (osteonecrosis of the jaw for which the underlying mechanism is unclear) or atypical femoral fractures (Kennel 2009; Khosla 2007). Most of these serious adverse events can be managed with rarely any long-term consequences (Tanvetyanon 2006). The severity can be directly related to the duration and intensity of treatment; therefore, it is important that in a preventive setting these interventions are used in suitable people for a defined period in relation to radiotherapy and assessment of baseline bone health.

How the intervention might work

Insufficiency fractures are usually related to underlying weakened bone, and the risk is increased in people with osteoporosis, rheumatoid arthritis, fibrous dysplasia (a condition wherein parts of bone are replaced by fibrous connective tissue), Paget's disease (a disorder characterised by areas of bone overgrowth),

osteogenesis imperfecta ('brittle bone disease'), osteomalacia (condition with inadequate mineralisation of bone, rickets in children) or hyperparathyroidism (excess parathyroid hormone (PTH) secretion usually caused by a parathyroid adenoma) (Blake 2004; Hosey 2008; Lourie 1982; Pentecost 1964).

The pathophysiology of radiotherapy-induced insufficiency fracture is not well understood, although data suggest that the incidence is increased in people with osteoporosis (Kim 2012; Park 2011). Therefore, interventions that target osteoporosis could potentially be effective.

Calcium and vitamin D optimise mineralisation of bone. Furthermore, trials with bisphosphonates that demonstrate reduction in fracture risk in postmenopausal women were carried out in the presence of optimal calcium and vitamin D levels (reviewed in NICE TA160 and NICE TA161).

Bisphosphonates, denosumab, calcitonin (a hormone produced by the thyroid gland, which opposes the actions of PTH), strontium (a drug with an antiresorptive effect) and teriparatide (a recombinant PTH) reduce the incidence of fracture in people with osteoporosis by preventing bone resorption or promoting bone formation or a combination of the two (reviewed in NICE TA160 and NICE TA161). Hormone replacement therapies (oestrogen and testosterone) may be used to improve bone density if hormonal deficiency is present.

There are no specific data available on treatment for radiotherapy-induced insufficiency fracture. However, if people undergoing pelvic radiotherapy have low vitamin D or hormone levels or underlying osteoporosis, providing optimal bone strength with a combination of the above could theoretically reduce the incidence of insufficiency fracture and avascular necrosis.

Insufficiency fractures are associated with increased mortality and morbidity (Bliuc 2009; Taillandier 2003). Therefore, the aim of pharmacological interventions is to prevent insufficiency fractures from occurring during or after radiotherapy, thus potentially reducing mortality and morbidity and improving QoL and participant-reported outcome measures.

Why it is important to do this review

Recognition that pelvic insufficiency fractures are a consequence of pelvic radiotherapy is increasing. Insufficiency fractures can lead to significant and prolonged morbidity in terms of pelvic/back pain and immobility, which, in turn, is associated with a variety of complications, including infection and pressure sores.

The clinical features of pelvic insufficiency fractures may be confused with those of metastatic or recurrent disease, leading to potentially unnecessary investigations, interventions and anxiety, all of which have a consequent impact on resources.

Currently, the UK has approximately two million cancer survivors, and this figure is projected to rise to four million by 2040 (Maddams 2012). Long-term consequences of cancer treatment vary significantly in severity and prevalence, but, as the number of cancer survivors increase, strategies to reduce the risk of developing these problems become more relevant. For people receiving pelvic radiotherapy, there is a need to identify possible therapeutic interventions that may reduce the incidence of radiation-induced pelvic insufficiency fracture. A systematic review of published studies examining the effects of these interventions

has not previously been undertaken and could inform the development of clinical guidelines, which, in turn, would benefit both people with cancer and healthcare systems.

OBJECTIVES

To assess the effects of pharmacological interventions for preventing insufficiency fractures and avascular necrosis in adults over 18 years of age undergoing pelvic radiotherapy.

Secondary endpoints include assessing effects on bone mineral density (BMD), fracture risk, and quality of life and reviewing adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including conference abstracts of RCTs, from which sufficient data could be obtained.

As few RCTs on pharmacological interventions were expected, we included non-randomised studies with concurrent comparison groups: for example, quasi-randomised trials, cluster RCTs, non-randomised trials, prospective cohort studies and case series of 30 or more participants.

We excluded case-control studies and case series of fewer than 30 participants.

Types of participants

People aged 18 years or older undergoing radical pelvic radiotherapy (external beam, brachytherapy, or both) as part of their anticancer treatment for a primary pelvic malignancy, including gynaecological (cervix or uterus), lower gastrointestinal (anal or rectal) and urological (prostate or bladder) malignancies. We excluded people with bone metastases.

Types of interventions

Pharmacological interventions provided at any stage before or during pelvic radiotherapy including

one or more of the following:

- calcium supplements;
- vitamin D supplements;
- bisphosphonates: alendronate, alendronic acid, etidronate, ibandronate, risedronate, zoledronate, pamidronate;
- selective oestrogen receptor modulators: raloxifene;
- hormone replacement: oestrogen replacement therapy, hormone replacement therapy;
- combined oestrogen and progesterone oral contraceptive pill;
- testosterone replacement: testosterone undecanoate, testosterone, esterised testosterone compounds;
- strontium ranelate;
- teriparatide;
- denosumab; and
- calcitonin.

Trials compared pharmacological interventions with no pharmacological interventions or compared alternative types of interventions.

We ensured that pooling of data for pharmacological interventions was appropriate and did not combine drugs that were different in composition. This potentially involved multiple comparisons. This review analysed those comparisons studied to date but in the future may be split to analyse each individual pharmacological intervention compared with placebo or standard care.

Types of outcome measures

Primary outcomes

- Insufficiency fractures and avascular necrosis developing within five years after completion of pelvic radiotherapy as determined by accepted radiological appearances on magnetic resonance imaging (MRI)/computed tomography (CT) imaging.

Secondary outcomes

- Bone mineral density (BMD) changes as determined by dual-energy x-ray absorptiometry (DEXA) (bone density scan), quantitative CT, quantitative MRI or ultrasound scanning and changes in fracture risk assessed using the FRAX score (method for calculating fracture risk) within five years after completion of radiotherapy.
- Changes in bone turnover markers, including serum alkaline phosphatase, bone-specific alkaline phosphatase, serum osteocalcin, serum type 1 procollagen (C-terminal/N-terminal: C1NP or P1NP), urinary hydroxyproline, urinary total pyridinoline (PYD), urinary free deoxypyridinoline (DPD), urinary collagen type 1 cross-linked N-telopeptide (NTX), urinary or serum collagen type 1 cross-linked C-telopeptide (CTX), bone sialoprotein (BSP) and tartrate-resistant acid phosphatase 5b.
- QoL measured using a scale that was validated through reporting of norms in a peer-reviewed publication, including participant-reported bone symptoms and participant outcomes.
- Mortality, specifically cancer-related and overall mortality.
- Adverse effects and compliance with pharmacological interventions, including those related to a specific agent or route of delivery.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 4, 2017) in the Cochrane Library;
- MEDLINE (Ovid) 1946 to April week 1 2017;
- Embase (Ovid) 1980 to 2017 week 16;
- DARE to April 2017.

The CENTRAL, MEDLINE and Embase search strategies are presented in [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#). All relevant articles were identified on PubMed and the 'related articles' feature was used to carry out a further search for newly published articles. Reports were sought in all languages and translations carried out as necessary.

Searching other resources

Unpublished and grey literature

For ongoing trials, we searched MetaRegister (www.controlled-trials.com), Physicians Data query (nci.nih.gov), www.ClinicalTrials.com (www.clinicaltrials.gov), and www.cancer.gov/clinicaltrials. If ongoing trials were identified that had not been published, we planned to approach the principal investigators to request relevant data. We searched conference proceedings and abstracts through ZETOC (zetoc.mimas.ac.uk) and WorldCat Dissertations.

Handsearches

We handsearched citation lists of included studies and previous systematic reviews to identify further relevant studies.

Data collection and analysis

Selection of studies

Two review authors (QM, KG) independently assessed all titles and abstracts retrieved by electronic searching to determine relevance and eligibility. We excluded reports that did not meet the inclusion criteria. Where there was insufficient information to make a decision based on the title and abstract, we obtained the full article. Two review authors independently assessed the full text of potentially relevant references to ensure they met the eligibility criteria. Any diversity of opinion was resolved through discussion between the two review authors and with recourse to a third review author as necessary. We documented reasons for exclusion of studies in the [Characteristics of excluded studies](#) table. Multiple reports of the same study were linked to ensure no data were included in the meta-analysis more than once.

Data extraction and management

We devised, piloted and modified as required a data collection form to facilitate data collection from the included studies. Two review authors (QM, KG) undertook the process of data extraction independently and discussed any discrepancies between themselves, consulting a third review author if needed. We recorded the following information for each trial:

- year of publication, country of origin and source of funding;
- participant details, number of participants, gender, age, inclusion and exclusion criteria;
- details of bone health:
 - BMD using validated measures;
 - fracture risk assessment derived from a validated tool (e.g. FRAX score); and
 - biochemical measures (including vitamin D, alkaline phosphatase, calcium, phosphate, P1NP and CTX);
- cancer diagnosis including type, stage, previous surgery and co morbidities;
- details of cancer treatment (including dose, volume, fractionation of external beam radiotherapy and details of brachytherapy, chemotherapy and surgery);
- details of cancer treatment delivery (including completion of planned treatment, unplanned hospital stay, breaks to radiotherapy and number of cycles of chemotherapy);
- details of pharmacological interventions (including type of intervention, timing in relation to radiotherapy, route of

intervention, length of intervention, quantity delivered and adverse effects);

- details of bone symptoms (including toxicity scores, participant-reported outcome measure score or other symptom-based questionnaires or interview scores);
- details of QoL measures including participant-reported outcomes;
- details of clinical outcomes, including unplanned hospital stay, recurrence of cancer, survival and mortality.

Details of primary and secondary outcomes collected included the time points at which they were collected and reported.

Assessment of risk of bias in included studies

We assessed risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011). Risk of bias was rated for each study in the following areas:

- random sequence generation and allocation concealment;
- allocation concealment;
- blinding;
- complete outcome data;
- selective outcome reporting;
- other sources of bias.

Individual 'risk of bias' items are detailed in [Appendix 4](#).

Measures of treatment effect

For dichotomous outcomes, we used the risk ratio (RR) and for continuous outcomes, we used the mean difference (MD) between treatment arms. Where studies measured outcomes on different scales, for example, bone symptoms and toxicity scores, we used standardised mean difference (SMD). For time-to-event data, we used the hazard ratio (HR). We presented 95% confidence intervals (CI).

Unit of analysis issues

Unit of analysis issues could arise due to multiple observations for the same outcome, for example, repeated measurements of bone symptoms over time. We reviewed short- and long-term bone symptoms or toxicity, as defined in the outcomes section, as these were clinically significant endpoints. If there were still multiple time points within these two discrete categories, we addressed this either by obtaining individual participant data to determine the individual's trend over time or by selecting a single time point within the two time categories for analysis.

We handled studies with multiple control groups by combining all relevant control groups into a single group for comparison with the intervention. Studies with multiple intervention groups were combined into a single group for comparison with the control group where possible. If this was not possible, then we performed a pair-wise comparison with shared intervention or control groups divided out approximately evenly among comparisons. For dichotomous outcomes, we divided the number of events and the total number of participants. For continuous outcomes, we divided only the total number of participants while the means and standard deviations (SD) were unchanged.

Dealing with missing data

In studies with missing outcome data, we contacted study authors to seek the relevant information. Missing data was not imputed and therefore available case analysis was performed.

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the types of participant, interventions and outcomes in each study. There were insufficient data to perform a meta-analysis. In future updates, we plan to conduct meta-analyses where studies reported similar comparisons for the outcome measures. We planned to assess statistical heterogeneity using the Chi² test to determine whether the observed differences in results were compatible with chance alone, and use the I² statistic to determine the impact of heterogeneity on the meta-analysis (Deeks 2001; Higgins 2003).

Assessment of reporting biases

There were insufficient studies to assess reporting biases. In future updates of this review, we plan to use funnel plots to make visual assessment of whether small-study effects may be present and whether publication bias could be one of the number of explanations for small-study effects.

Data synthesis

A meta-analysis could not be conducted due to heterogeneity in terms of populations, interventions and outcomes. Studies using brachytherapy alone versus studies using external beam radiotherapy were felt unsuitable for direct comparison. This was due to the significantly higher radiation exposure to bone using external beam radiotherapy compared to organ-confined treatment in brachytherapy, which would be associated with differences in pattern of toxicity between these treatments.

In future updates of this review, we plan to use the generic inverse variance method for dichotomous data if the published paper only reported odds ratio or RR and its standard error. We would also use the generic inverse variance method for continuous data if the published paper only reported the difference between the means of the two groups and the standard error of this difference and we are unable to obtain any raw data from the author.

Using generic inverse variance in future reviews would also facilitate the analysis of cluster randomised and non-randomised trials if appropriate (DerSimonian 1986). RCTs and non-randomised studies would only be combined in a meta-analysis if the non-randomised studies were properly analysed and at low risk of bias.

We presented the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). We created a 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro GDT. We used the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We downgraded the evidence from high quality by one level for serious (or by two levels for very serious) concerns for each limitation.

Subgroup analysis and investigation of heterogeneity

Due to the lack of studies for meta-analysis, we performed no subgroup analyses. In future updates of this review, where data allow, we plan to undertake the following subgroup analyses:

- comparisons by primary tumour;
- comparison by use of hormones;
- comparison by use of steroids;
- comparison by cancer treatment modalities, including external beam radiotherapy, brachytherapy, chemotherapy, surgery and a combination of these.

Sensitivity analysis

There were insufficient studies to perform sensitivity analysis. We noted missing data in the selected studies and contacted trial authors to request individual participant data to obtain missing

information and resolve uncertainties regarding outcome data. As we were unable to obtain adequate data, we interpreted the available data with caution.

RESULTS

Description of studies

Results of the search

An initial database search and three further top-up searches identified 4300 titles. Of these, we excluded 4234 during title and abstract searches. We reviewed 66 full papers and excluded 65 as 13 were duplications and 52 did not meet eligibility criteria. This left 1 which we felt suitable for inclusion, ([Kachnic 2013](#)). Handsearching of references identified seven papers, of which one was eligible for inclusion into the review ([Denham 2014](#)). This, combined with the one paper from the database search, led to two studies, both RCTs, selected for review. See [Figure 1](#).

Figure 1. Study flow diagram.

Included studies

We included two RCTs and no non-randomised studies.

Kachnic 2013

This was a multicentred, double-blind randomised placebo-controlled trial of 96 men with high-grade or locally advanced,

non-metastatic prostate cancer commencing radiotherapy plus luteinising hormone-releasing hormone (LHRH) agonist to determine if the addition of zoledronic acid would prevent any bone fractures, and benefit QoL and BMD over three years ([Kachnic 2013](#)).

The primary outcome was freedom from any bone fracture measured from the date of randomisation to date of documented bone fracture(s). Other outcomes included percentage change in BMD from baseline to 36 months and change in QoL as measured by the Functional Assessment of Cancer Therapy-General (FACT-G) and Euro-QoL (EQ-5D) scores. Details of the radiotherapy were not described or made available after contacting the authors. They excluded people with osteoporosis at baseline.

The trial did not meet its annual accrual goals (target accrual 1272) and, due to the low annual accrual, the trial was closed early. The reasons for low accrual were not detailed or obtainable from the authors. One hundred and nine participants were randomised, 57 to the intervention group and 52 to the control group. One participant was excluded from the intervention group (participant declined treatment). Participants were stratified according to BMD T-scores and duration of LHRH agonist treatment.

All participants received vitamin D and calcium in addition to starting the LHRH agonist and radiotherapy. Participants randomised to the intervention received intravenous (IV) zoledronic acid 4 mg from the start of radiotherapy and every six months for three years. DEXA scans were performed before treatment, and at 18 and 36 months and QoL questionnaires were completed at baseline, then every six months to three years.

Twelve participants withdrew consent and subsequently 96 were analysed (50 in the intervention group). Participant characteristics were balanced, most Zubrod performance score (a measure of performance status) 0 (94%), Gleason 8 to 10 (grading of prostate cancer) (69%) and node negative (89%).

Denham 2014

This was a multicentred, RCT using a 2×2 factorial design investigating the impact of adjuvant androgen suppression and zoledronic acid on BMD and fractures in men with locally advanced non-metastatic prostate cancer. The primary outcome was incidence of thoracolumbar fractures at three years. Other outcomes included incident non-spinal fractures and a sub study reviewing changes in BMD at the hip from baseline to two and four years after randomisation (Denham 2014).

Participants were randomised to one of four treatment groups in the 2×2 study design. All participants received six months of leuporelin (22.5 mg every three months intramuscularly) at randomisation, five months before radiotherapy to the prostate and seminal vesicles. The control group received no further treatment (short-term androgen suppression (STAS)). The intervention group received an additional 12 months' leuporelin (intermediate-term androgen suppression (ITAS)). In addition, participants in each group were randomised to receive zoledronic acid 4 mg IV every three months or no bisphosphonate for 18 months from randomisation (STAS plus zoledronic acid and ITAS plus zoledronic acid). Therefore, interventions were started five months prior and continued during and after radiotherapy. Details of the radiotherapy dose and schedule were not published or made available to the review authors.

Fractures were assessed on thoracolumbar x-rays performed at baseline and at three years. Assessments were done locally with a central review, with both assessors blinded to the treatment groups. Incident fractures were defined as one or more vertebrae

with new loss of height at three years amounting to 1 or more Genant grades (a classification of vertebral fractures). Incident fractures were considered 'new' if not present at baseline and 'worsened' if a prevalent fracture existed at baseline. There were no CT or MRI scans used within the trial protocol to define the nature of these fractures. Other incident non-spinal fractures were documented from participant self-reporting at each follow-up visit. Details were not given regarding how or where these fractures were diagnosed and what imaging modality was used. BMD was assessed in the sub study group before treatment, and at two and four years using a DEXA scan. The results of the DEXA scan were independently reviewed by an expert blinded to the trial groups.

A total of 1071 participants were treated for a median follow-up of 5.6 years. All four groups were balanced in number and characteristics (STAS: 268 men; ITAS: 268 men; STAS plus zoledronic acid: 268 men; ITAS plus zoledronic acid: 267 people). Only 905 participants had evaluable x-rays for the primary endpoint at three years and 166 (15.5%) were not evaluable due to commencing secondary therapeutic interventions (58 men), death (32 men), withdrawal from the study (28 men) and other reasons not specified (44 men).

Baseline fracture risk was calculated using a composite variable based method. High risk was defined as presence of one or more of the following factors: aged 80 years or older, history of non-spinal or symptomatic vertebral fractures, diabetes, alcohol intake 21 or more standard drinks/week, current smoker and asymptomatic thoracolumbar fractures. Participants without these factors were deemed a low fracture risk. This fracture risk assessment method is non-validated compared to other methods such as the FRAX score.

Overall, this study was investigating spinal bone fractures in relation to androgen deprivation rather than radiation-related insufficiency fractures. Fractures were assessed using x-rays done at baseline and at three years. Incident non-spinal fractures were based on self-reporting at follow-up with no clear imaging protocol defining these further.

See [Characteristics of included studies](#) table.

Excluded studies

There were 52 studies and 13 duplicates which were excluded as they did not meet the inclusion criteria. Within these studies, we considered 26 in detail as they were closely related to the review topic but were still excluded for multiple reasons as detailed in the [Characteristics of excluded studies](#) table. Of these studies, 7 were preclinical animal studies, 5 trials did not include radiotherapy for all participants, 6 studies only reported retrospective outcomes, 9 studies did not have an intervention group, 11 trials did not report fractures related specifically to radiotherapy and 4 studies had an intervention unrelated to radiotherapy. Two studies involved an intervention group, but the participants were undergoing radiotherapy for bone metastases so were excluded from further analyses. Two studies were initially short listed for inclusion (Smith 2003 and Smith 2012), but as outlined below, both were subsequently considered unsuitable for analysis.

Smith 2003

This was a multicentre double-blind randomised, placebo-controlled trial investigating whether zoledronic acid prevented

bone loss due to androgen deprivation therapy in men with non-metastatic prostate cancer (Smith 2003).

The primary outcome was percentage change in BMD in the lumbar spine from baseline to one year, assessed using DEXA scans. Other outcomes included changes in BMD of the femoral neck, trochanter (upper part of the femur), total hip and non-dominant forearm sites and incidence of new or worsening vertebral fractures. Subanalyses of the primary endpoint were done with respect to baseline BMD T-score.

All participants starting androgen deprivation therapy with a gonadotrophin-releasing hormone agonist were randomised to receive zoledronic acid 4 mg IV (55 men) or placebo (51 men), every three months for one year. The study drug was given in a double-blind method, and all participants received calcium supplements and multivitamins including vitamin D.

DEXA scans were performed at baseline and 12 months, spine x-rays were taken at baseline, 12 weeks, 36 weeks and 12 months with a central review and the assessor was blinded to the treatment groups. There were no CT or MRI scans performed to further clarify the nature of any fracture. Serum chemistry was performed at baseline, every 12 weeks and at end of the study. Adverse events and laboratory results were graded for severity using Common Terminology Criteria for Adverse Events (CTCAE).

Of the 106 men randomised, 27 were excluded from the efficacy analysis due to good clinical practice violations or because post-treatment BMD measurements were not performed or evaluable. Compliance to zoledronic acid was 86% and to the placebo was 82%. Participant characteristics were balanced between groups and, of note, 33 participants (31%) had undergone prior radiotherapy. Radiotherapy details were not given or made available by authors. Analysis was performed on the whole group and not specifically in men who had undergone radiotherapy.

There was a reported increase in lumbar spine BMD at one year in the intervention group ($P < 0.001$) and there was a difference in mean percentage BMD change at one year between the two groups by 7.8% (95% CI 5.6% to 10%; $P < 0.001$). The difference in change of lumbar spine BMD between the two treatments was also noted in the subgroups: participants with normal BMD (T scores -1 or greater) and in participants with low baseline BMD (T scores less than -1 and greater than -3).

The intervention group demonstrated increased BMD in the femoral neck, trochanter and total hip from baseline. The mean difference in percentage change from baseline was reported between the intervention and placebo for the femoral neck, trochanter and total hip ($P < 0.001$) but not the non-dominant forearm.

There were five (9%) radiologically diagnosed new or worsening vertebral fractures in the zoledronic acid group and three (5.8%) in the placebo group ($P = 0.29$). Details on the location of these vertebral fractures were not reported or available and no detailed CT/MRI imaging was used to characterise the nature of these fractures.

The mean total testosterone decreased to castrate levels in both groups at 12 weeks and remained suppressed until the end of the study period. The mean prostate-specific antigen (PSA) decreased

from baseline in both groups but there were no significant differences between the zoledronic acid and placebo groups in the mean change from baseline in testosterone or PSA.

There were adverse events grade 3 to 4 in 24% in the intervention group and 39% in the placebo group. Two participants in the intervention group withdrew from the study due to adverse events, which were not described in further detail. No QoL data were collected.

Overall, this study focused on the change in BMD in relation to androgen deprivation and the impact of zoledronic acid in increasing BMD rather than prevention of radiation-related insufficiency fractures. Not all participants received radiotherapy, and the intervention was done at a later time point to radiotherapy. Fractures were only assessed by x-ray imaging rather than CT/MRI and details of the nature of the fractures were not available. However, the study did show that the intervention resulted in an increase in BMD at one year compared to placebo, but the results were not specific to radiation-related insufficiency fractures and, therefore, this study was excluded from further analysis and review.

Smith 2012

This trial described an international phase 3 double-blind randomised placebo-controlled trial to determine if denosumab would increase bone metastasis-free survival, delay onset of bone metastasis and influence prostate cancer-specific progression-free survival in men with non-metastatic castrate-resistant prostate cancer (Smith 2012).

The primary outcome was bone metastasis-free survival using time to first bone metastasis or death. Other outcomes included overall survival, prostate-specific progression-free survival and changes in PSA and bone turnover markers.

Men deemed castrate resistant with a risk of bone metastases were randomised to receive the intervention (denosumab 120 mg subcutaneously every four weeks) or placebo (subcutaneously every four weeks) in a double-blind design. All participants received calcium and vitamin D unless they had hypercalcaemia. Antineoplastic treatments deemed necessary were allowed prior to enrolment and during the study. The study treatment was continued until bone metastases occurred and follow-up continued for three years after discontinuation of treatment.

Radioisotope bone scans were performed every four months and yearly radiographic skeletal surveys to detect bone metastases. On suspicion of metastases, further imaging with CT/MRI/x-rays were done to confirm bone metastasis. Assessment of imaging was performed centrally and assessors were masked to the trial groups.

Following randomisation, 716 participants received intervention and 716 received placebo. Baseline characteristics were well balanced between the two groups. About 5% of participants in both groups had received prior chemotherapy, and 45% had received local therapy (radiotherapy, prostatectomy, or both). Further details on numbers receiving radiotherapy were not reported or available from the authors. Details of the radiotherapy delivered and timing in relation to the study treatment were also not detailed.

Median bone metastases-free survival was 29.5 months in the intervention group (95% CI 25.4 to 33.3) and 25.2 months in the

placebo group (95% CI 22.2 to 29.5), representing a 15% decrease in risk (HR 0.85, 95% CI 0.73 to 0.98; $P = 0.028$).

Denosumab was associated with a delayed time to first bone metastasis of 33.2 months (95% CI 29.5 to 38) compared with placebo that was 29.5 months (95% CI 22.4 to 33.1). Overall survival was similar in both groups. Adverse events were similar in both groups except osteonecrosis of the jaw (5% with denosumab versus 0% with placebo) and hypocalcaemia (2% with denosumab versus less than 1% with placebo). These events were higher with denosumab and are clinically important, though statistical significance was not given.

Bone turnover markers were decreased with denosumab compared with placebo. Although the authors did not present the full data, they reported P values of < 0.001 for each comparison.

Overall, the findings of this study suggested that denosumab improved bone metastasis-free survival and was associated with prolonged time to first bone metastasis and fewer symptomatic bone metastases than placebo in castrate-resistant prostate cancer. There was no consideration in this study of bone fragility and non-metastatic bone toxicity. Details of radiotherapy were incomplete and other parameters of BMD were not reported. Bone turnover markers did show an improvement with denosumab, but this was in relation to prostate cancer progression rather than bone morbidity specifically from radiotherapy.

Risk of bias in included studies

The risk of bias summary is given in [Figure 2](#) and judgements about each risk of bias item presented as a percentage across all included studies is shown in [Figure 3](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

One of the included RCTs described their method of randomisation and allocation concealment and was, therefore, at low risk of bias (Denham 2014). The other RCT reported the method of randomisation but not allocation concealment (Kachnic 2013). Further information was not obtained after contacting the authors, so this study was rated as unclear risk of selection bias.

Blinding

One RCT was double-blind and placebo controlled and was at low risk of performance and detection bias (Kachnic 2013). The remaining RCT did not use placebo or blinding of participants, though did have assessors blinded to the intervention groups (Denham 2014). This study was at high risk of performance bias, though low risk of detection bias.

Incomplete outcome data

The included studies were both rated at low risk of attrition bias. It was noted that in one RCT there was only 58% data on QoL (Kachnic 2013), and so this was rated as high risk.

Selective reporting

The included studies both reported on the primary outcomes and secondary outcomes as set in their methods sections. The location of fractures was not detailed in one RCT and scores relating to QoL were not provided, so this trial was at high risk of reporting bias.

Other potential sources of bias

Both studies did not fully describe the radiotherapy techniques used in the groups. The dose, delivery of treatment (conformal, intensity modulated, brachytherapy) and, therefore, volume of pelvis irradiated could influence the pattern of bone fractures, changes in BMD and risk of avascular necrosis. Studies were also heterogeneous in other aspects so meta-analysis was not performed and the results were reported as a narrative.

One RCT had an imbalance in the sub study groups reporting on changes in BMD, where one group may have had higher risk factors for osteoporosis, which could have biased the results (Denham 2014). The results reported by Kachnic 2013 would need to be interpreted with caution as the study had inadequate accrual therefore lacked statistical power to detect differences.

Effects of interventions

See: [Summary of findings for the main comparison Pharmacological intervention compared with no intervention for prevention of radiation-related insufficiency fractures and avascular necrosis](#)

It was impossible to summarise the outcomes of interest (including incidence of insufficiency fractures and change in BMD) due to heterogeneity in data collection using different methods and different endpoints. See [Summary of findings for the main comparison](#) for a summary and GRADE assessment.

Insufficiency fractures and avascular necrosis

One study reported two fractures, one in each group (Kachnic 2013). There was no reported difference in freedom from any bone fracture ($P = 0.95$). Details of the location and nature of these fractures and how they were detected were not published or made available from the study authors when requested.

The other RCT reported 72 non-spinal fractures, 34 in the control group, 38 in the intervention group (Denham 2014). They found no significant differences in incidence ($P = 0.64$) or four-year cumulative probability of non-spinal fractures ($P = 0.26$) between groups. Radiotherapy-related fractures were not specifically described in the non-spinal fractures. The authors provided detail that only three fractures were near the radiation field but details of the treatment groups for these participants were not provided. They reported only one case of avascular necrosis but did not state in which group this case occurred. Overall, they reported no significant difference in the incidence of spinal or non-

spinal fractures based on duration of androgen deprivation or use of zoledronic acid.

Both studies reported a low number of fractures but the details of the fracture (location, nature) were not described and hence there was uncertainty regarding these being insufficiency fractures from radiotherapy. Details of the nature of fractures and their relation to radiotherapy were not available for either study. The imaging and investigation for fractures also did not meet the review criteria and, for these reasons, further analyses regarding the interventions affecting risk of insufficiency fractures was not possible.

Bone mineral density and fracture risk

Both studies reported improvements in BMD. One RCT reported these changes in BMD at 36 months after randomisation with zoledronic acid (Kachnic 2013). They assessed BMD in different areas and there was a significant change in BMD at the left hip (1% with zoledronic acid versus -8% with control; $P = 0.0002$), lumbar spine (6% with zoledronic acid versus -5% with control; $P < 0.0001$) and left femoral neck (3% with zoledronic acid versus -8% with control; $P = 0.00007$). The other RCT included a sub study to assess the change in total hip BMD at 24 and 48 months from randomisation (Denham 2014). For the six-month androgen deprivation group, there was no change in BMD at 24 months (0.6%; $P = 0.18$) but there was a significant increase at 48 months (1.8%; $P = 0.003$). In the 12-month androgen deprivation group, there was no significant change in BMD at 24 months (0.5%; $P = 0.41$) and a tendency towards significance at 48 months (1.2%; $P = 0.09$). As different time points and different areas were used to measure changes in BMD, meta-analysis was not possible. We judged the evidence on BMD to be of very low certainty and the differences described not likely to be clinically significant.

One RCT reported fracture risk (Denham 2014). They reported that, using multivariate analysis and adjusting for the baseline fracture risk, participants receiving ITAS were at highest risk of non-spinal fractures compared with participants receiving STAS (HR 2.55; $P = 0.013$). Both groups receiving zoledronic acid had non-significantly higher risks than those receiving STAS. However, the analyses relating to fracture risk were based on non-validated methods and found no significant reduction in fracture risk with zoledronic acid. For this reason, no further analyses of the data were done and the evidence on reduction on fracture risk was judged to be very low certainty.

Bone turnover markers

The two RCTs did not report changes in bone turnover markers between the control and intervention groups.

Quality of life

One RCT reported on QoL measures (Kachnic 2013), and suggested there were no differences in QoL between groups. However, this study accrued only a small number of participants and only 58% of QoL data were obtained at 36 months, so there is likely to be a lack of statistical power to detect any true differences. Denham 2014 did not collect QoL data.

Neither trial reported bone symptoms or unplanned hospital stays.

Mortality

Neither trial reported cancer-specific mortality or overall mortality.

Adverse events

In one RCT, zoledronic acid was discontinued by 19 participants either due to adverse events (four participants), death (one participant), disease progression (four participants), participant refusal (three participants) and other reasons (seven participants) (Kachnic 2013). The mean dose per person was 5.5 of 6 infusions (92%). They reported no grade 4 adverse events or osteonecrosis of the jaw.

The other RCT reported good compliance to STAS (99%), ITAS (85%) and zoledronic acid (77%) (Denham 2014). The authors reported zoledronic acid missed doses were to avoid the increased risk of mandibular osteonecrosis due to unplanned dental extractions. Osteonecrosis of the mandible was noted in two participants (0.4%) on 18 months of zoledronic acid.

DISCUSSION

There were limited studies addressing the review question of pharmacological interventions that may prevent insufficiency fractures and avascular necrosis following pelvic radiotherapy. The studies we included, while meeting our inclusion criteria, provided evidence of very low certainty. Both studies predominantly reported changes in BMD and fractures in relation to androgen deprivation rather than pelvic radiotherapy. Imaging techniques to detect fractures were either not detailed (Kachnic 2013), or did not meet our specified criteria including MRI/CT (Denham 2014). There was limited information relating to the nature, location and type of fractures reported in both trials and, therefore, interpretation of these outcomes being insufficiency radiation-related fractures was taken with caution. Details of the radiotherapy were not available in either study, as the focus in these studies was related to bone changes in relation to androgen deprivation rather than radiotherapy. The radiation dose, volume and technique influence the incidence and location of insufficiency fractures and, without this information, the aetiology of the reported fractures was unknown and these data, therefore, must be interpreted with caution.

The outcomes reported in both studies were for men with prostate cancer receiving androgen deprivation and the results of the intervention might not be applicable to other cancers in which pelvic radiotherapy is used. The secondary outcomes relating to changes in BMD, bone turnover markers and cancer outcomes were not analysed. There was heterogeneity in reporting of BMD; such as different time points and different sites for BMD evaluation. The area evaluated for BMD was often non-pelvic and, therefore, outcomes may have been more in relation to androgen deprivation rather than localised changes resulting from radiotherapy. Neither study reported bone turnover markers or overall mortality.

The pathophysiology of radiation-related bone changes are almost certainly different to those causing osteoporosis. In vitro and animal studies suggest that radiation causes changes in bone vascularity, and altered osteoblastic and osteoclastic function. Pharmacological interventions aimed at treating osteoporosis and loss of BMD from hormone imbalances may not necessarily be transferable as methods to alter the pathological processes involved in radiation-related bone loss and fractures.

Conducting the review identified several preclinical animal studies that did not meet our inclusion criteria but specifically

investigated interventions to reduce radiation-related bone toxicity (Sarhaddi 2013; Felice 2015; Tchanque-Fossuo 2013; Misra 2016). These animal studies included investigation of amifostine, a radioprotective drug aiming to preserve vascularity and improve bone healing related to radiotherapy. Sarhaddi 2013 demonstrated that rats receiving amifostine with radiotherapy showed greater fracture healing and increased bone vascularity compared with rats treated with radiotherapy alone and rats that received no irradiation. Donneys 2013 investigated the effect of desferrioxamine in radiation-induced fractures using rat models. They compared three groups, non-irradiated fractures, irradiated fractures and irradiated fractures treated with desferrioxamine. They found desferrioxamine significantly increased callus size, strength and mineralisation compared with irradiated fractures. The callus metrics were restored to a level demonstrating no statistical difference from control non-irradiated fractures. The authors concluded that administration of desferrioxamine may have the potential for clinical translation as a new treatment paradigm for radiation-induced fractures.

One novel small animal radiation research platform has been developed that is able to replicate focal radiotherapy. Studies using this method to irradiate the proximal metaphyseal region (bone growth plate) of rats demonstrated the efficacy of PTH 1-34 therapy in preventing radiation-induced apoptosis of osteoblasts and osteoclasts maintaining the integrity of bone (Chandra 2014). In these studies, in contrast to previous murine studies (Keenawinna 2013, Willey 2010), alendronate was of no benefit. The relevance of this to pelvic radiotherapy in humans remains to be determined.

One phase 1 study did not meet the inclusion criteria for review but involved people with vertebral metastases treated with high-dose radiotherapy in combination with zoledronic acid (Pichon 2016). This study provided evidence that zoledronic acid plus radiotherapy was safe and could be investigated further as an intervention in people without bone metastases with a view to reducing radiation-induced bone loss.

One excluded study specifically investigated zoledronic acid during radiotherapy to assess the effect on radiation-induced collagen bone loss (Gierloff 2015). Forty participants receiving radiotherapy for bone metastases were randomised to either zoledronic acid before or after radiotherapy. Urine samples measuring the bone metabolites hydroxylispyridinoline and lysylpyridinoline were used as markers for early radiation-induced bone degradation. The results suggested that participants receiving zoledronic acid at the start of radiotherapy had significantly lower excretion of bone metabolites than participants receiving zoledronic acid after radiotherapy and, therefore, this could indicate the drug has properties in lowering radiation-induced bone loss that may be due to osteoclastic activity. While this study was not undertaken in people with non-metastatic cancer receiving pelvic radiotherapy, the results showed promise of the drug having activity in reducing radiation-related bone damage, if used early in treatment, which may warrant formal investigation in prospective trials in people undergoing pelvic radiotherapy.

Summary of main results

The evidence on zoledronic acid to prevent radiotherapy-related bone complications was of a very low certainty and there was no evidence on other pharmacological interventions that might do so. Findings suggesting that zoledronic acid might improve BMD

were very uncertain because the mechanism of the effect of the intervention might be to address androgen deprivation-specific rather than radiotherapy-specific bone loss.

Overall completeness and applicability of evidence

We found no studies addressing interventions specifically aimed at preventing insufficiency fractures and avascular necrosis from pelvic radiotherapy. While there were data suggesting improvement in BMD with zoledronic acid, there was incomplete information relating to this intervention and radiation-related bone loss or radiation techniques and doses used. Kachnic 2013 did not fully accrue and the study was underpowered to detect a difference in fractures, bone density and QoL. There were imbalances in one RCT in relation to the subgroups used for reviewing BMD outcomes (Denham 2014). Both studies were of men with prostate cancer treated with androgen suppression and, therefore, the evidence reported would be applicable in this group but might not be relevant in other cancers treated with pelvic radiotherapy such as rectal, cervical, endometrial and anal cancers.

Quality of the evidence

The certainty of the evidence was very low for all outcomes in the included studies (GRADE Working Group; Summary of findings for the main comparison). There was heterogeneity between the trials in reporting outcomes at different time points, poor reporting of results and limitations in study methodology. Despite the included studies being RCTs, they were downgraded for other factors such as source of bias in the design, imprecision of results and indirectness of evidence.

Both studies had limitations in their design and precision of results, either due to imbalances in the study population (Denham 2014) or incomplete data and lack of statistical power due to poor accrual (Kachnic 2013). There was heterogeneity in the methods for assessing outcomes and in the time points of reporting. One study did not describe the method of identifying fractures (Kachnic 2013), and the other study utilised plain x-rays rather than cross-sectional imaging, which may have limited identification of early insufficiency fractures (Denham 2014). There was a lack of detail relating to the pelvic radiotherapy used and there were a small number of events reported for insufficiency fracture and avascular necrosis across both studies.

The included studies both assessed the effect of zoledronic acid in a prostate cancer population and, therefore, may not be applicable to other patient groups receiving pelvic radiotherapy, which may involve a wider radiation field (gynaecological or rectal cancer). The groups receiving androgen deprivation therapy may also be influencing the outcomes in terms of affecting BMD and risk of fractures. The evidence was indirect, as it may be reporting effects restricted to this population and may not relate to women, people undergoing pelvic radiotherapy for other cancers and people not receiving androgen deprivation.

Potential biases in the review process

The review was undertaken to identify interventions in the prevention of radiation-related insufficiency fractures. Many papers did not use a clear definition to described fractures and, therefore, we have assumed, unless clearly stated, that the fractures were not specific to radiation. This may have potentially

led to exclusion of some data from the review, which was not clarified easily through contacting authors.

Agreements and disagreements with other studies or reviews

There were no other reviews found addressing the same outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Based on this review, there is a lack of evidence relating to interventions to prevent insufficiency fractures and avascular necrosis associated with pelvic radiotherapy in adults. The included studies were not meta-analysed as they lacked power to detect a difference (Kachnic 2013) or were not specifically reporting on radiation-related bone fractures (Denham 2014).

There is a lack of evidence relating to interventions improving bone mineral density in relation to radiation-induced bone loss. All studies considered were focused on reporting bone mineral density changes in relation to hormone deprivation.

Implications for research

This review highlights the need for prospective clinical trials using interventions prior to or during (or both) radiotherapy to

prevent radiation-related bone morbidity, insufficiency fractures and avascular necrosis. Radiation-related bone fractures need to be reported differently to other types of fracture. Interventions addressing bone mineral density and fracture risk should use validated tools to allow future comparison of interventions. The preclinical studies involving amifostine and desferrioxamine show some promise as agents which could be a feature in clinical trials specifically acting on the pathway related to radiation-related bone toxicity.

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REFERENCES

References to studies included in this review

Denham 2014 {published data only (unpublished sought but not used)}

Denham JW, Nowitz M, Joseph D, Duchesne G, Spry NA, Lamb DS, et al. Impact of androgen suppression and zoledronic acid on bone mineral density and fractures in the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) randomized controlled trial for locally advanced prostate cancer. *British Journal of Urology International* 2014;**114**:344-53.

Kachnic 2013 {published data only (unpublished sought but not used)}

Kachnic LA, Pugh SL, Tai P, Smith M, Gore E, Shah AB, et al. RTOG 0518: randomized phase III trial to evaluate zoledronic acid for prevention of osteoporosis and associated fractures in prostate cancer patients. *Prostate Cancer and Prostatic Diseases* 2013;**16**:382-6.

References to studies excluded from this review

Acil 2013 {published data only}

Acil Y, Gierloff M, Behrens C, Moller B, Gassling V, Niehoff P, et al. Effects of zoledronate on irradiated bone in vivo: analysis of the collagen types I, V and their cross-links lysylpyridinoline, hydroxylysylpyridinoline and hydroxyproline. *Calcified Tissue International* 2013;**92**:251-60.

Blery 2014 {published data only}

Blery P, Corre P, Malard O, Sourice S, Pilet P, Amouriq Y, et al. Evaluation of new bone formation in irradiated areas using association of mesenchymal stem cells and total fresh bone marrow mixed with calcium phosphate scaffold. *Journal of Materials Science. Materials in Medicine* 2014;**25**:2711-20.

Butoescu 2014 {published data only}

Butoescu V, Tombal B. Practical guide to bone health in advanced prostate cancer. *Canadian Journal of Urology* 2014;**21**(21 (Suppl 1)):84-92.

Coleman 2014 {published data only}

Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J. Bone health in cancer patients: ESMO clinical practice guidelines. *Annals of Oncology* 2014;**25** (Suppl 3):iii124-37.

Donneys 2013 {published data only}

Donneys A, Ahsan S, Perosky JE, Deshpande SS, Tchanque-Fossuo CN, Levi B, et al. Deferoxamine restores callus size, mineralization, and mechanical strength in fracture healing after radiotherapy. *Plastic and Reconstructive Surgery* 2013;**131**:711e-9e.

Felice 2015 {published data only}

Felice PA, Gong B, Ahsan S, Deshpande SS, Nelson NS, Donneys A, et al. Raman spectroscopy delineates radiation-induced injury and partial rescue by amifostine in bone: a murine mandibular model. *Journal of Bone and Mineral Metabolism* 2015;**33**(3):279-84.

Gierloff 2015 {published data only}

Gierloff M, Reutemann M, Gulses A, Niehoff P, Wiltfang J, Acil Y. Effects of zoledronate on the radiation-induced collagen breakdown: a prospective randomized clinical trial. *Clinical & Translational Oncology* 2015;**17**(6):454-61.

Higham 2015 {published data only}

Higham CE, Faithful S. Bone health and pelvic radiotherapy. *Clinical Oncology* 2015;**27**:668-78.

Israeli 2007 {published data only}

Israeli RS, Rosenberg SJ, Saltzstein DR, Gottesman JE, Goldstein HR, Hull GW, et al. The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy. *Clinical Genitourinary Cancer* 2007;**5**(4):271-7.

Mehmood 2013 {published data only}

Mehmood Q, Beardwood M, Swindell R, Greenhalgh S, Wareham T, Barraclough L, et al. Insufficiency fractures in patients treated with pelvic radiotherapy and chemotherapy for uterine and cervical cancer. *European Journal of Cancer Care* 2013;**23**:43-50.

Michaelson 2007 {published data only}

Michaelson MD, Kaufman DS, Lee H, McGovern FJ, Kantoff PW, Fallon MA, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *Journal of Clinical Oncology* 2007;**25**(9):1038-42.

Misra 2016 {published data only}

Misra J, Mohanty ST, Madan S, Fernandes JA, Hal Ebetino F, Russell RG, et al. Zoledronate attenuates accumulation of DNA damage in mesenchymal stem cells and protects their function. *Stem Cells* 2016;**34**(3):756-67.

Oh 2014 {published data only}

Oh D, Huh SJ. Insufficiency fracture after radiation therapy. *Radiation Oncology Journal* 2014;**32**(4):213-20.

Otani 2016 {published data only}

Otani K, Teshima T, Ito Y, Kawaguchi Y, Konishi K, Takahashi H, et al. Risk factors for vertebral compression fractures in preoperative chemoradiotherapy with gemcitabine for pancreatic cancer. *Radiotherapy and Oncology* 2016;**118**:424-9.

Ottanelli 2015 {published data only}

Ottanelli S. Prevention and treatment of bone fragility in cancer patient. *Clinical Cases in Mineral and Bone Metabolism* 2015;**12**(2):116-29.

Pichon 2016 {published data only}

Pichon B, Campion L, Delpon G, Thillays F, Carrie C, Collier P, et al. High-dose hypofractionated radiation therapy for noncompressive vertebral metastases in combination with zoledronate: a phase 1 study. *International Journal of Radiation Oncology, Biology, Physics* 2016;**96**(4):840-7.

Ramlov 2017 {published data only}

Ramlov A, Pederson EM, Rohl L, Worm E, Fokdal L, Lindegaard JC, et al. Risk factors for pelvic insufficiency fractures in locally advanced cervical cancer following intensity modulated radiation therapy. *International Journal of Radiation Oncology, Biology, Physics* 2017;**97**(5):1032-9.

Rizzoli 2013 {published data only}

Rizzoli R, Body JJ, Brandi ML, Cannata-Andia J, Chappard D, El Maghraoui A, et al. Cancer-associated bone disease. *Osteoporosis International* 2013;**24**:2929-53.

Sarhaddi 2013 {published data only}

Sarhaddi D, Tchanque-Fossuo CN, Poushanchi B, Donneys A, Deshpande SS, Weiss DM, et al. Amifostine protects vascularity and improves union in a model of irradiated mandibular fracture healing. *Plastic and Reconstructive Surgery* 2013;**132**(6):1542-9.

Shahinian 2005 {published data only}

Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *New England Journal of Medicine* 2005;**352**:154-64.

Smith 2001 {published data only}

Smith MR, McGovern FJ, Zietman A, Fallon MA, Hayden DL, Schonfeld DA, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *New England Journal of Medicine* 2001;**345**:948-55.

Smith 2003 {published data only}

Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinners N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for non-metastatic prostate cancer. *Journal of Urology* 2003;**169**:2008-12.

Smith 2009 {published data only}

Smith MR, Egerdie B, Toriz NH, Feldman R, Tammela TLJ, Saad F, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *New England Journal of Medicine* 2009;**361**(8):745-55.

Smith 2012 {published data only}

Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* 2012;**379**:39-46.

Tchanque-Fossou 2013 {published data only}

Tchanque-Fossuo CN, Donneys A, Sarhaddi D, Poushanchi B, Deshpande SS, Weiss DM, et al. Amifostine prophylaxis on bone densitometry, biomechanical strength and union in mandibular pathologic fracture repair. *Bone* 2013;**57**(1):56-61.

Wei 2016 {published data only}

Wei RL, Jung BC, Manzano W, Sehgal V, Klempner SJ, Lee SP, et al. Bone mineral density loss in thoracic and lumbar vertebrae following radiation for abdominal cancers. *Radiotherapy and Oncology* 2016;**118**:430-6.

Additional references
Abe 1992

Abe H, Nakamura M, Takahashi S, Maruoka S, Ogawa Y, Sakamoto K. Radiation-induced insufficiency fractures of the pelvis: evaluation with 99mTc-methylene diphosphonate scintigraphy. *American Journal of Roentgenology* 1992;**158**(3):599-602.

Andreyev 2005

Andreyev J. Gastrointestinal complications of pelvic radiotherapy: are they of any importance?. *Gut* 2005;**54**(8):1051-4.

Bauer 2000

Bauer M, Thabault P, Estok D, Christiansen C, Platt R. Low-dose corticosteroids and avascular necrosis of the hip and knee. *Pharmacoepidemiology and Drug Safety* 2000;**9**(3):187-91.

Baxter 2005

Baxter N, Habermann E, Tepper J, Durham S, Vernig B. Risk of pelvic fractures in older women following pelvic irradiation. *JAMA* 2005;**294**(20):2587-93.

Blake 2004

Blake SP, Connors AM. Sacral insufficiency fracture. *British Journal of Radiology* 2004;**77**:891-6.

Bliss 1996

Bliss P, Parsons CA, Blake PR. Incidence and possible aetiological factors in the development of pelvic insufficiency fractures following radical radiotherapy. *British Journal of Radiology* 1996;**69**:548-54.

Bliuc 2009

Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA* 2009;**301**(5):513-21.

Blomlie 1996

Blomlie V, Rofstad EK, Talle K, Sundfr K, Winderen M, Lien HH. Incidence of radiation-induced insufficiency fractures of the female pelvis: evaluation with MR imaging. *American Journal of Roentgenology* 1996;**167**(5):1205-10.

Chandra 2014

Chandra A, Lin T, Tribble MB, Zhu J, Altman, Tseng WJ, et al. PTH1-34 alleviates radiotherapy-induced local bone loss by improving osteoblast and osteocyte survival. *Bone* 2014;**67**:33-40.

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2nd Edition. London (UK): BMJ Publication Group, 2001.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177-88.

Dzik-Jurasz 2001

Dzik-Jurasz ASK, Brooker S, Husband JE, Tait D. What is the prevalence of symptomatic or asymptomatic femoral head osteonecrosis in patients previously treated with chemoradiation? A magnetic resonance study of anal cancer patients. *Clinical Oncology* 2001;**13**(2):130-4.

Erickson 2000

Erickson BA, Murray KJ, Erickson SJ, Carrera GF. Radiation-induced pelvic bone complications: an underestimated sequelae of pelvic irradiation. *International Journal of Radiation Oncology, Biology, Physics* 2000;**48**(3 Suppl 1):126.

GRADE Working Group

GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**:1490-4.

Hauer-Jensen 2003

Hauer-Jensen M, Wang J, Denham JW. Bowel injury: current and evolving management strategies. *Seminars in Radiation Oncology* 2003;**13**(3):357-71.

Herman 2009

Herman MP, Kopetz S, Bhosale PR, Eng C, Skibber JM, Rodriguez-Bigas MA, et al. Sacral insufficiency fractures after preoperative chemoradiation for rectal cancer: incidence, risk factors, and clinical course. *International Journal of Radiation Oncology, Biology, Physics* 2009;**74**(3):818-23.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *British Medical Journal* 2003;**327**:557-60.

Higgins 2011

Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hopewell 2003

Hopewell JW. Radiation-therapy effects on bone density. *Medical and Pediatric Oncology* 2003;**41**(3):208-11.

Hosey 2008

Hosey RG, Fernandez MMF, Johnson DL. Evaluation and management of stress fractures of the pelvis and sacrum. *Orthopedics* 2008;**4**:383-5.

Huh 2002

Huh SJ, Kim B, Kang MK, Lee JE, Lim DH, Park W, et al. Pelvic insufficiency fracture after pelvic irradiation in uterine cervix cancer. *Gynecologic Oncology* 2002;**86**(3):264-8.

Ikushima 2006

Ikushima H, Osaki K, Furutani S, Yamashita K, Kishida Y, Kudoh T, et al. Pelvic bone complications following radiation

therapy of gynecologic malignancies: clinical evaluation of radiation-induced pelvic insufficiency fractures. *Gynecologic Oncology* 2006;**103**(3):1100-4.

İğdem 2010

İğdem S, Alço G, Ercan T, Barlan M, Ganiyusufoğlu K, Ünalın B, et al. Insufficiency fractures after pelvic radiotherapy in patients with prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2010;**77**(3):818-23.

Jenkins 1995

Jenkins PJ, Sebag Montefiore DJ, Arnott SJ. Hip complications following chemoradiotherapy. *Clinical Oncology* 1995;**7**(2):123-6.

Keenawinna 2013

Keenawinna L, Oest ME, Mann KA, Spadaro J, Damron TA. Zoledronic acid prevents loss of trabecular bone after focal irradiation in mice. *Radiation Research* 2013;**180**(1):89-99.

Kennel 2009

Kennel KA, Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. *Mayo Clinic Proceedings* 2009;**84**(7):632-8.

Khosla 2007

Khosla S, Burr D, Cauley J. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *Journal of Bone and Mineral Research* 2007;**22**(10):1479-91.

Kim 2012

Kim HJ, Boland PJ, Meredith DS, Lis E, Zhang Z, Shi W, et al. Fractures of the sacrum after chemoradiation for rectal carcinoma: incidence, risk factors, and radiographic evaluation. *International Journal of Radiation Oncology, Biology, Physics* 2012;**84**(3):649-99.

Kirwan 2003

Kirwan JM, Symonds P, Green JA, Tierney J, Collingwood M, Williams CJ. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. *Radiotherapy and Oncology* 2003;**68**(3):217-26.

Kwon 2008

Kwon JW, Huh SJ, Yoon YC, Choi S-H, Jung JY, Oh D, et al. Pelvic bone complications after radiation therapy of uterine cervical cancer: evaluation with MRI. *American Journal of Roentgenology* 2008;**191**(4):987-94.

Langendam 2013

Langendam MW, Akl EA, Dahm P, Glasziou P, Guyatt G, Schünemann HJ. Assessing and presenting summaries of evidence in Cochrane Reviews. *Systematic Reviews* 2013;**2**:81.

Lawton 2012

Lawton CA, Shook S, Smith M, Tripp P, Shah AB, Martin A, et al. RTOG Protocol 05-18: a phase III randomized trial to evaluate the efficacy of zoledronic acid for the prevention of osteoporosis and associated fractures in patients receiving radiation therapy (RT) and long-term luteinizing hormone-

releasing hormone (LHRH) agonist for high-grade and/or locally advanced prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2012;**84**(3):S369.

Lourie 1982

Lourie H. Spontaneous osteoporotic fracture of the sacrum: an underrecognized syndrome of the elderly. *JAMA* 1982;**248**:715-7.

Maddams 2012

Maddams J, Utley M, Møller H. Projections of cancer prevalence in the United Kingdom, 2010-2040. *British Journal of Cancer* 2012;**107**:1195-202.

Meador 2014

Meador N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. *Systematic Reviews* 2014;**3**:82.

Mears 2011

Mears SC, Berry DJ. Outcomes of displaced and nondisplaced pelvic and sacral fractures in elderly adults. *Journal of the American Geriatric Society* 2011;**59**(7):1309-12.

NICE TA160

NICE. TA160 Alendronate, Etidronate, Risedronate, Raloxifene and Strontium Ranelate for the Primary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women. London (UK): National Institute for Health and Clinical Excellence, 2011.

NICE TA161

NICE. Osteoporosis - Secondary Prevention Including Strontium Ranelate: Guidance. TA161. London (UK): National Institute for Health and Clinical Excellence, January 2011.

Ogino 2003

Ogino I, Okamoto N, Ono Y, Kitamura T, Nakayama H. Pelvic insufficiency fractures in postmenopausal woman with advanced cervical cancer treated by radiotherapy. *Radiotherapy and Oncology* 2003;**68**(1):61-7.

Oh 2008

Oh D, Huh SJ, Nam H, Park W, Han Y, Lim DH, et al. Pelvic insufficiency fracture after pelvic radiotherapy for cervical cancer: analysis of risk factors. *International Journal of Radiation Oncology, Biology, Physics* 2008;**70**(4):1183-8.

Ono 1992

Ono K, Tohjima T, Komazawa T. Risk factors of avascular necrosis of the femoral head in patients with systemic lupus erythematosus under high-dose corticosteroid therapy. *Clinical Orthopaedics and Related Research* 1992;**277**:89-97.

Park 2011

Park SH, Kim JC, Lee JE, Park IK. Pelvic insufficiency fracture after radiotherapy in patients with cervical cancer in the era of PET/CT. *Radiation Oncology Journal* 2011;**29**(4):269-76.

Pentecost 1964

Pentecost RL, Murray RA, Brindley HH. Fatigue, insufficiency and pathologic fractures. *JAMA* 1964;**187**:111-4.

Schmeler 2010

Schmeler KM, Jhingran A, Iyer RB, Sun CC, Eifel PJ, Soliman PT, et al. Pelvic fractures after radiotherapy for cervical cancer. *Cancer* 2010;**116**(3):625-30.

Shih 2013

Shih KK, Folkert MR, Kollmeier MA, Abu-Rustum NR, Sonoda Y, Leitao MM, et al. Pelvic insufficiency fractures in patients with cervical and endometrial cancer treated with post-operative pelvic radiation. *Gynecologic Oncology* 2013;**128**(3):540-3.

Taillandier 2003

Taillandier J. Mortality and functional outcomes of pelvic insufficiency fractures in older patients. *Joint Bone Spine* 2003;**70**(4):287-9.

Tanvetyanon 2006

Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Annals of Oncology* 2006;**17**(6):897-907.

Tchanque-Fossuo 2013

Tchanque-Fossuo CN, Donneys A, Sarhaddi D, Poushanchi B, Deshpande SS, Weiss DM, et al. Amifostine prophylaxis on bone densitometry, biomechanical strength and union in mandibular pathologic fracture repair. *Bone* 2013;**57**(1):56-61.

Tokumaru 2012

Tokumaru S, Toita T, Oguchi M, Ohno T, Kato S, Niibe Y, et al. Insufficiency fractures after pelvic radiation therapy for uterine cervical cancer: an analysis of subjects in a prospective multi-institutional trial, and cooperative study of the Japan Radiation Oncology Group (JAROG) and Japanese Radiation Oncology Study Group (JROSG). *International Journal of Radiation Oncology, Biology, Physics* 2012;**84**:195-200.

West 2009

West CML, Davidson S. Measurement tools for gastrointestinal symptoms in radiation oncology. *Current Opinion in Supportive and Palliative Care* 2009;**3**:36-40.

Willey 2010

Willey JS, Livingston EW, Robbins ME, Bourland JD, Tirado-Lee L, Smth-Sielicki H, et al. Risedronate prevents early radiation-induced osteoporosis in mice at multiple skeletal locations. *Bone* 2010;**46**(1):101-11.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Denham 2014

Methods	Randomised controlled trial.
Participants	Total number, n = 905 evaluable out of 1071 Men aged >18 years. Histologically confirmed prostate cancer, no lymph node or distant metastases. T2b-4, T2a with Gleason score ≥ 7 or PSA ≥ 10 .
Interventions	AS + RT and AS for 12 months. AS + RT and zoledronic acid for 18 months. AS + RT, AS for 12 months and zoledronic acid for 18 months.
Outcomes	Primary: vertebral fractures at 3 years. Secondary: BMD at hip after 2 and 4 years, incident non-spinal fractures.
Notes	Intervention started at randomisation. AS + zoledronic acid started 5 months prior RT.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation using minimisation methods.
Allocation concealment (selection bias)	Low risk	Central randomisation using minimisation methods.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Interventions not blinded to participants or personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to intervention groups.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only low levels of missing data (10%).
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.
Other bias	High risk	Imbalances at baseline for the BMD sub study group, with 1 group having higher baseline osteoporosis risk. This may bias secondary outcomes reported.

Kachnic 2013

Methods	Double-blind, placebo-controlled, randomised controlled trial.
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Kachnic 2013 (Continued)

Participants	<p>Total number, n = 96</p> <p>Men aged > 18 years.</p> <p>Histologically confirmed prostate cancer, no distant metastases.</p> <p>High-risk groups defined as:</p> <ul style="list-style-type: none"> • $\geq$ T3; • < T3 + Gleason > 8; • < T3, Gleason 7 and PSA $\geq$ 15; • < T3, Gleason < 7 and PSA $\geq$ 20. • Any N stage
Interventions	<p>Control: RT with vitamin D/calcium (daily, for 3 years).</p> <p>Intervention: RT with vitamin D/calcium + intravenous zoledronic acid 4 mg (6 monthly, for 3 years).</p>
Outcomes	<p>Primary: freedom from ANY bone fracture.</p> <p>Secondary: percentage change in BMD from 0 to 36 months, QoL changes (Functional Assessment of Cancer Therapy - General and Euro-QoL scores).</p>
Notes	<p>Intervention started with RT and continued for 3 years.</p> <p>All participants received vitamin D and calcium.</p> <p>Study failed to accrue number needed to demonstrate statistically significant differences.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using permuted blocks.
Allocation concealment (selection bias)	Unclear risk	No details mentioned regarding allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, placebo-controlled trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to intervention groups.
Incomplete outcome data (attrition bias) All outcomes	High risk	Primary outcome data available but QoL data only complete for 8%, which would bias QoL outcomes.
Selective reporting (reporting bias)	High risk	No details given regarding site or nature of fractures, QoL scores not detailed.
Other bias	High risk	Poor accrual to study reducing statistical power.

AS: androgen suppression; BMD: bone mineral density; PSA: prostate-specific antigen; QoL: quality of life; RT: radiotherapy.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Acil 2013	Preclinical investigational animal study.
Blery 2014	Preclinical investigational animal study addressing treatment of radiation bone toxicity.
Butoescu 2014	No interventional group, outcomes not radiotherapy specific.
Coleman 2014	No intervention group, outcomes not radiotherapy specific.
Donneys 2013	Preclinical investigational animal study.
Felice 2015	Preclinical investigational animal study.
Gierloff 2015	Participants having radiotherapy for metastatic disease.
Higham 2015	Overview, no intervention group.
Israeli 2007	Radiotherapy not used in any participants, outcomes not radiotherapy specific.
Mehmood 2013	Retrospective outcomes, no intervention group.
Michaelson 2007	Intervention not timed in relation to radiotherapy, outcomes not radiotherapy specific.
Misra 2016	Preclinical investigational animal study.
Oh 2014	Retrospective outcomes, no intervention group.
Otani 2016	Retrospective outcomes, no intervention group.
Ottanelli 2015	Interventions on bone health, not radiotherapy specific.
Pichon 2016	Participants with intervention to bone metastases.
Ramlov 2017	Retrospective outcomes, no intervention group.
Rizzoli 2013	No intervention group, outcomes are not radiotherapy specific.
Sarhaddi 2013	Preclinical investigational animal study.
Shahinian 2005	Retrospective outcomes, no intervention group, outcomes not radiotherapy specific.
Smith 2001	Radiotherapy not given to all participants, intervention not timed in relation to radiotherapy, outcomes not radiotherapy specific.
Smith 2003	Radiotherapy not given to all participants, intervention not timed in relation to radiotherapy, outcomes not radiotherapy specific, imaging of fractures did not include CT/MRI. See Smith 2003 under Excluded studies .
Smith 2009	Study excluded people who had received radiotherapy, outcomes not radiotherapy specific.
Smith 2012	Radiotherapy not given to all participants, intervention not timed in relation to radiotherapy, outcomes not radiotherapy specific. See Smith 2012 under Excluded studies .
Tchanque-Fossou 2013	Preclinical investigational animal study.

Study	Reason for exclusion
Wei 2016	Retrospective outcomes, no intervention group.

CT: computed tomography; MRI: magnetic resonance imaging.

APPENDICES

Appendix 1. CENTRAL search strategy

```
#1 MeSH descriptor: [Fractures, Bone] explode all trees
#2 fracture*.mp.
#3 bone* near/5 (break or broke*)
#4 MeSH descriptor: [Femur Head Necrosis] this term only
#5 femur head necrosis
#6 avascular necrosis
#7 (bone* near/5 (fragility or fragile))
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Radiotherapy] explode all trees
#10 radiotherap* or brachytherap* or IMRT
#11 radiat* or irradiat*
#12 Any MeSH descriptor with qualifier(s): [Radiotherapy - RT]
#13 #9 or #10 or #11 or #12
#14 Any MeSH descriptor with qualifier(s): [Drug therapy - DT]
#15 MeSH descriptor: [Calcium, Dietary] explode all trees
#16 MeSH descriptor: [Vitamin D] explode all trees
#17 MeSH descriptor: [Diphosphonates] explode all trees
#18 MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees
#19 MeSH descriptor: [Hormone Replacement Therapy] explode all trees
#20 MeSH descriptor: [Contraceptives, Oral] explode all trees
#21 MeSH descriptor: [Testosterone] explode all trees
#22 (calcium or vitamin D or bisphosphonate* or alendronate or alendronic acid or etidronate or ibandronate or risedronate or zoledronate or pamidronate or (selective adj (oestrogen or estrogen) adj receptor modulator*) or raloxifene or hormone replacement or ((oestrogen or estrogen) adj replacement therapy) or oral contraceptive pill or testosterone or sustanon or strontium ranelate or teriparatide or denosumab or calcitonin)
#23 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
#24 #8 and #13 and #23
```

Appendix 2. MEDLINE search strategy

```
1 exp Fractures, Bone/
2 fracture*.mp.
3 (bone* adj5 (break or broke*)).mp.
4 Femur Head Necrosis/
5 femur head necrosis.mp.
6 avascular necrosis.mp.
7 (bone* adj5 (fragility or fragile)).mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp Radiotherapy/
10 (radiotherap* or brachytherapy or IMRT).mp.
11 (radiat* or irradiat*).mp.
12 radiotherapy.fs.
13 9 or 10 or 11 or 12
14 drug therapy.fs.
15 Calcium, Dietary/
16 exp Vitamin D/
17 exp Diphosphonates/
18 exp Selective Estrogen Receptor Modulators/
19 exp Hormone Replacement Therapy/
```

20 exp Contraceptives, Oral/
 21 exp Testosterone/
 22 (calcium or vitamin D or bisphosphonate* or alendronate or alendronic acid or etidronate or ibandronate or risedronate or zoledronate or pamidronate or (selective adj (oestrogen or estrogen) adj receptor modulator*) or raloxifene or hormone replacement or ((oestrogen or estrogen) adj replacement therapy) or oral contraceptive pill or testosterone or sustanon or strontium ranelate or teriparatide or denosumab or calcitonin).mp.
 23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
 24 8 and 13 and 23

key:

mp = Title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier

Appendix 3. Embase Ovid search strategy

1 exp fracture/
 2 fracture*.mp.
 3 (bone* adj5 (break or broke*)).mp.
 4 femur head necrosis/
 5 femur head necrosis.mp.
 6 avascular necrosis.mp.
 7 (bone* adj5 (fragility or fragile)).mp.
 8 1 or 2 or 3 or 4 or 5 or 6 or 7
 9 exp radiotherapy/
 10 (radiotherap* or brachytherapy or IMRT).mp.
 11 (radiat* or irradiat*).mp.
 12 rt.fs.
 13 9 or 10 or 11 or 12
 14 dt.fs.
 15 calcium intake/
 16 exp vitamin D/
 17 exp bisphosphonic acid derivative/
 18 selective estrogen receptor modulator/
 19 exp hormone substitution/
 20 exp oral contraceptive agent/
 21 androgen therapy/
 22 (calcium or vitamin D or bisphosphonate* or alendronate or alendronic acid or etidronate or ibandronate or risedronate or zoledronate or pamidronate or (selective adj (oestrogen or estrogen) adj receptor modulator*) or raloxifene or hormone replacement or ((oestrogen or estrogen) adj replacement therapy) or oral contraceptive pill or testosterone or sustanon or strontium ranelate or teriparatide or denosumab or calcitonin).mp.
 23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
 24 8 and 13 and 23
 25 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
 26 24 not 25

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

fs=floating subheading

Appendix 4. Risk of bias

Random sequence generation

- Low risk of bias (e.g. participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers).
- High risk of bias (e.g. participants assigned to treatments on basis of date of birth or clinic ID number or surname, or no attempt made to randomly assign participants).
- Unclear risk of bias (e.g. not reported, information not available).

Allocation concealment

- Low risk of bias (e.g. allocation sequence could not be foretold).
- High risk of bias (e.g. allocation sequence could be foretold by participants, investigators or treatment providers).
- Unclear risk of bias (e.g. not reported).

Blinding of participants and personnel

- Low risk of bias if participants and personnel were adequately blinded.
- High risk of bias if participants were not blinded to the intervention that they received.
- Unclear risk of bias if this was not reported or was unclear.

Blinding of outcomes assessors

- Low risk of bias if outcomes assessors were adequately blinded.
- High risk of bias if outcomes assessors were not blinded to the interventions that participants received.
- Unclear risk of bias if this was not reported or was unclear.

Incomplete outcome data

We recorded the proportion of participants whose outcomes were not reported at the end of the study. We coded a satisfactory level of loss to follow-up for each outcome as:

- low risk of bias if less than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment groups;
- high risk of bias if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment groups; and
- unclear risk of bias if loss to follow-up was not reported.

Selective reporting of outcomes

- Low risk of bias (e.g. review reported all outcomes specified in the protocol).
- High risk of bias (e.g. suspected that outcomes were selectively reported).
- Unclear risk of bias (e.g. unclear whether outcomes were selectively reported).

Other bias

- Low risk of bias: no suspicion of any other source of bias and trial appeared to be methodologically sound.
- High risk of bias: suspected that the trial was prone to an additional bias.
- Unclear risk of bias: uncertain whether an additional bias may have been present.

Non-randomised studies

We assessed the risk of bias in non-randomised controlled trials in accordance with four additional criteria concerning cohort selection and comparability of treatment groups.

Relevant details of criteria for assignment of participants to treatments

- Low risk of bias (e.g. yes).
- High risk of bias (e.g. no).
- Unclear risk of bias.

Representative group of participants who received the experimental intervention

- Low risk of bias if representative of adults undergoing pelvic radiotherapy.
- High risk of bias if groups of participants were selected.
- Unclear risk of bias if selection of group was not described.

Representative group of participants who received the comparison intervention

- Low risk of bias if drawn from the same population as the experimental cohort.
- High risk of bias if drawn from a different source.
- Unclear risk of bias if selection of group was not described.

No differences between the two groups or differences controlled for, in particular with reference to age, gender, type/dose of radiotherapy, use of chemotherapy and performance status

- Low risk of bias if at least two of these characteristics were reported.
- High risk of bias if the 2 groups differed and differences were not controlled for.
- Unclear risk of bias if fewer than two of these characteristics were reported even if no other differences were noted between the groups and other characteristics were controlled for.

CONTRIBUTIONS OF AUTHORS

All the named review authors have been involved in the development of this review.

DECLARATIONS OF INTEREST

Qurrat U van den Blink: none known.

Kate Garcez: none known.

Caroline C Henson: none known.

Susan E Davidson: none known.

Claire E Higham: none known.

SOURCES OF SUPPORT**Internal sources**

- No source, Other.

None to declare

External sources

- No source, Other.

None to declare

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The planned database searches did not include electronic searches of AMED, BNI or CINAHL as it was felt the other databases would encompass data required for the review.

The planned subgroup analyses in relation to age, gender, type of radiotherapy and baseline fracture risk were removed from the final review as it was felt there was limited primary data for the review and meaningful analyses of these subgroups would not be possible.

INDEX TERMS**Medical Subject Headings (MeSH)**

Androgen Antagonists [*therapeutic use]; Bone Density Conservation Agents [*therapeutic use]; Calcium Compounds [therapeutic use]; Diphosphonates [*therapeutic use]; Femur Head Necrosis [*prevention & control]; Fractures, Stress [etiology] [*prevention & control]; Imidazoles [*therapeutic use]; Pelvic Neoplasms [radiotherapy]; Prostatic Neoplasms [*radiotherapy]; Radiation Injuries [*prevention & control]; Vitamin D [therapeutic use]; Vitamins [therapeutic use]; Zoledronic Acid

MeSH check words

Adult; Humans; Male