Systematic review

The effect of radiotherapy, and radiotherapy combined with bisphosphonates or RANK ligand inhibitors on bone quality in bone metastases. A systematic review

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ABSTRACT

Purpose: The role of radiotherapy in stabilizing metastatic bones is unclear. This systematic review assessed the effects of (1) radiotherapy, (2) radiotherapy combined with bisphosphonates, and (3) radiotherapy combined with RANK ligand (RANKL) inhibitors on bone quality and bone strength in bone metastases originating from solid tumors.

Methods: Pubmed, EMBASE and the Cochrane Library were searched. Any type of study design and type and dose of radiotherapy, bisphosphonates and RANKL inhibitors were allowed.

Results: 39 articles were identified. Animal studies showed that radiotherapy had similar effects on bone quality and strength as receiving no treatment, whereas adding bisphosphonates to radiotherapy restored bone quality and strength. In patient studies, bone density increased after radiotherapy and radiotherapy combined with bisphosphonates. However, due to the often non-optimal study design and study quality, it was unclear whether this increase could be attributed to these treatments. There was insufficient evidence to assess the additional effect of bisphosphonates or RANKL inhibitors.

Conclusion: Despite the clinical experience that radiotherapy is an effective treatment for bone metastases, there was no sufficient evidence for a positive effect on bone quality and fracture risk. Animal studies showed that adding bisphosphonates to radiotherapy restored bone quality and strength, whereas this was not proven in patients. There were no studies addressing the adjunct effect of RANKL inhibitors to radiotherapy. Although associated with several methodological, practical and ethical challenges, randomized controlled trials are needed.

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Metastatic bone disease is a common and severe complication in patients with advanced cancer. It develops in up to ∼75% of patients with advanced solid cancer [1]. Bone metastases are most often observed in patients with breast (65–75%) and prostate (65–75%) cancer, but also occur in other metastatic solid cancers [2]. Without treatment, patients with bone metastases may suffer from pain and other debilitating skeletal complications such as pathological fractures or, when vertebrae are affected, neurological complaints such as spinal cord compression [2,3]; all dramatically affecting the patients' quality of life [1,4]. In metastatic bone disease, the main goals of treatment are relief of pain and skeletal stabilization with preservation or restoration of (neurological) function, mobility, and quality of life [5].

According to current clinical guidelines, patients confronted with already fractured bones or having large impending lesions in weight bearing bones should be treated with surgical osteosynthesis for immediate stabilization [6–9]. From the perspective of the patient, however, it would be beneficial if metastatic lesions could be sufficiently stabilized using non-invasive treatments, such as local radiotherapy. Radiotherapy can be given either alone, or in combination with systemic therapies (e.g. anticancer treatments

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with chemotherapy or hormonal therapy, bisphosphonates, and RANK ligand (RANKL) inhibitors) to increase the bone strengthening effect.

Currently, clinicians have difficulties in assessing bony instability based on the available diagnostic imaging data [6,8,9] and both radiotherapy and systemic therapies are used widespread to palliate the lesions by reducing pain and, as a secondary effect, to increase the bone mass. As low bone density, such as in patients suffering from osteoporosis and metastatic bone disease, is a strong predictor for future fracture risk, therapeutically increasing bone density might result in a lower fracture risk [10,11]. Bone fractures are devastating events for patients with bone metastases, as bone fractures are accompanied by pain, stress and anxiety, need for surgery, decreased quality of life and can lead to complications such as spinal cord compression. In order to use non-invasive modalities for stabilization purposes, it should be determined whether these treatments are effective. And, if so, it should be established what treatment, or combination of treatments, is most effective in improving the bone quality and bone strength of affected bones.

Although radiotherapy has long been established as an effective local treatment for metastatic bone pain [5,12–16], its use in stabilizing affected bones is based merely on clinical experience. Scientific data underlining this stabilizing effect are scarce. Radiotherapy is thought to first reduce the bone mineral density (BMD) during a short period of time directly after radiotherapy, but subsequently induce re-calcification of the lesion, a process during which new bone is formed [17]. It is generally believed that, in patients responding to radiotherapy, about three months are necessary for the bone to be sufficiently strengthened [17].

In current practice, bisphosphonates (BPs) are also used to increase the bone mass and strength, to prevent future pathological fractures [18–21]. Furthermore, RANKL inhibitors inhibit osteoclast mediated bone resorption [22] and might, therefore, also play a role in increasing bone mass.

The general idea is that the newly formed bone induced by radiotherapy, bisphosphonates, and RANKL inhibitors strengthens the affected bone [23]. The effect of combining radiotherapy and BPs or RANKL inhibitors on bone quality is unknown. As these treatments have different mechanisms of action [24–26], they might have an additive or synergistic effect on the process of re-calcification of metastatically affected bones [27]. Consequently, these treatment combinations might prevent pathological fractures and accompanying neurological problems, depending on the anatomical localization of the lesion, more effectively.

A thorough analysis of the potentially stabilizing effect of non-invasive treatments for patients with metastatically affected bones can aid in the clinical treatment decision making process. Therefore, the aims of this systematic review are to assess the effects of (1) radiotherapy, (2) radiotherapy combined with bisphosphonates, and (3) radiotherapy combined with RANKL inhibitors, on bone quality and bone strength parameters in bone metastases originating from solid tumors.

Methods

Search strategy

PubMed, EMBASE and the Cochrane Library were searched (last search performed November 26th, 2015). No limits were used for PubMed and the Cochrane Library. The search in EMBASE was limited to articles, errata, and reviews. The search strategy included search terms and their synonyms for bone metastases, radiotherapy, bisphosphonates, RANKL inhibitors, bone mineral density, bone quality and bone strength. The search strategy was developed in collaboration with information specialists from the medical library of the Radboud university medical center Nijmegen, the Netherlands. The detailed search strategy is provided in Supplementary File A. In addition, reference lists of the included studies as well as relevant retrieved narrative and systematic reviews were screened for potentially missed papers.

Study selection

Original studies using radiotherapy, BPs and RANKL inhibitors of any type and dosage were allowed. Both human and animal studies were included. In addition, we allowed all types of study design.

In the screening stage, studies were evaluated based on title and abstract. Studies were excluded if they fulfilled one of the following criteria: (1) No primary study; (2) No bone metastases; (3) No or not only bone metastases originating from solid primary tumors; (4) None of the following as intervention(s): radiotherapy, radiotherapy vs. radiotherapy, radiotherapy vs. radiotherapy + BPs, radiotherapy + BPs, radiotherapy vs. radiotherapy + RANKL inhibitor, or radiotherapy + RANKL inhibitor. As we were not only interested in the 'end effect' (bone strength or fracture) but also in the changes in bone density, we decided that it would be better to have similar mechanisms of metastasizing or tumor growth. Therefore, we solely included studies on metastases originating from solid primary tumors. If eligibility for inclusion could not be decided based on abstract screening, the full text article was retrieved.

Subsequently, full text articles of the selected studies were evaluated for eligibility. Studies were excluded if they met any of criteria 1–4, or one of the following: (5) Article not in English, German, or Dutch; (6) Radiotherapy was not applied locally or directly to bone metastases; (7) None of the following outcome measures, or surrogate outcome measures, were reported: re-calcification, bone density, bone micro-architecture, bone strength, pathological fractures; (8) Outcome measures were not determined at the irradiated side. In addition, papers were excluded if the paper contained data also published in another included paper. In case of a sub study being part of the larger, original study, the original study was included. In case of reported preliminary data the most extended paper was included. Two reviewers (K.G., M.P.) independently screened titles and abstracts and selected full texts for eligibility. Disagreements were resolved by discussion and consensus and if necessary a third reviewer was consulted (Y.v.d.L.).

Data extraction

K.G. extracted the data onto a preset data extraction form. This form was pilot tested using 15 articles to check if all variables of interest were successfully extracted. After completing the data extraction, M.P. reviewed the data extraction form for completeness and accuracy. Next to bibliographic details, we collected data on study design (type of study, key exclusion criteria, number of patients/animals and lesions included, and time of assessment), patient characteristics (primary tumor site, treated site(s)), treatment, and methods used to measure the outcome measures of interest. Outcome measures related to bone quality and bone strength were divided into five principal outcome categories: (1) Radiologic response (any qualitative description of re-calcification), (2) bone density (any quantitative description of bone density), (3) micro-architecture, (4) bone strength, and (5) pathological fractures. Studies had to report on at least one of the defined outcome measure categories. When pathological fractures were reported, time to fracture was also extracted. Other time related parameters, such as follow-up time or survival time, were also extracted when studies reported on fracture rate. If data were only presented graphically, data were manually extracted from these graphs.

Quality assessment

The Quality Assessment Tool for Quantitative Studies developed by the Effective Public Health Practice Project was used to assess methodological quality [28]. Each study was rated as 'strong', 'moderate', or 'weak' on six individual components (selection bias, study design, confounders, blinding, data collection methods, withdrawal and dropouts). An overall global rating was then assigned to each study with studies classified as 'strong' (no weak ratings), 'moderate' (one weak rating), or 'weak' (two or more weak ratings). Two authors (K.G. and M.P.) rated the methodological quality of all studies independently. Disagreements were resolved by discussion.

Results

Study selection

The search strategy retrieved 3273 unique records. Subsequent selection procedure resulted in 37 eligible articles. Two additional relevant articles were found via cross-referencing. Thus, 39 studies [17,29–66] were included in this systematic review (Fig. 1). Vassiliou et al. [63,64] confirmed that both their studies contained unique patient cohorts and, therefore, both studies were included. Although the studies by Foerster et al. [39] and Schlampp et al. [54] had an overlap of about 80% in patient population, they reported on different outcome parameters. Therefore, both studies were included in this systematic review.

Study description and quality assessment

Descriptive data for the included studies are summarized in Supplementary File B. Of the 39 studies included, three were animal studies and 36 were patient studies. Overall, patient studies varied considerably in terms of study design, type and dose of radiotherapy and BP, type of primary tumor, and location of bone metastases. In addition, different definitions for similar outcome measures were used (Supplementary File B), similar outcome measures were quantified using different methods (Supplementary File B), and outcome measures were assessed at different time points after radiotherapy (Supplementary Files C–E). Seven of the 22 patient studies reporting on pathological fractures looked at pathological fractures as primary outcome measure.

Fig. 2 gives an overview of study quality assessment. Overall, four, 23 and 12 of the included studies were rated as 'strong', 'moderate', and 'weak', respectively. Seven studies stated that the allocation of the treatment to the treatment groups was randomized. However, only one of these studies mentioned the method of randomization used and provided sufficient details to adequately judge the method. The other six were thus defined as a controlled clinical trial instead of a randomized controlled clinical trial. Furthermore, 33 of the studies were rated as 'strong' on 'confounders', reflecting the absence of pre-treatment differences between groups. However, 21 out of these 33 studies contained a single intervention group. Therefore, these studies scored 'strong' on 'confounding', as there were no differences between groups. In addition, most prospective studies reported poorly on withdrawals
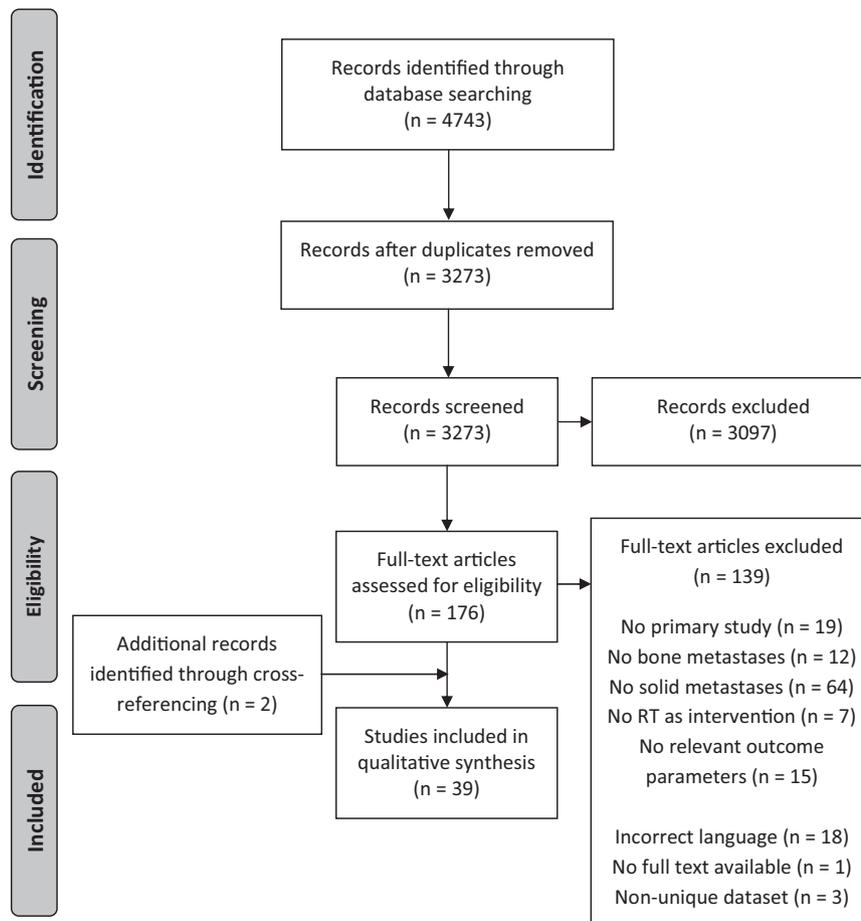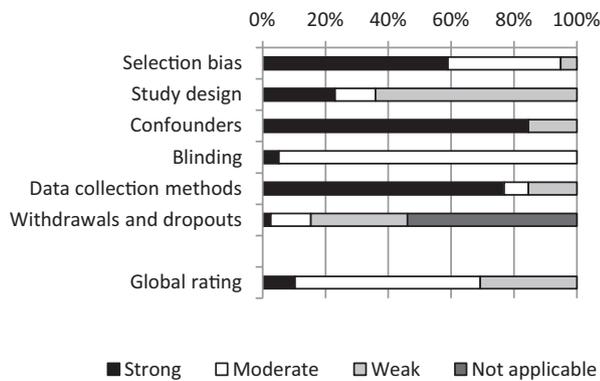

Fig. 1. Flow diagram of the systematic review literature search results.

Fig. 2. Quality assessment of the 39 included studies using the Quality Assessment Tool for Quantitative Studies [28]. Each study was rated as 'strong', 'moderate', or 'weak' on six individual components. An overall global rating was then assigned to each study with studies classified as 'strong' (no weak ratings), 'moderate' (one weak rating), or 'weak' (two of more weak ratings). The results are averaged per item.

and dropouts. The individual scores of each study are presented in Supplementary File F.

Animal studies

Three animal studies (Supplementary File C) investigated differences in bone quality between metastatic bone lesions treated with only radiotherapy and radiotherapy combined with BPs. Arrington et al. [29,30] used zoledronic acid (ZA) as BP and Krempien et al. [31] used chlodronate (CL). Combining ZA with radiotherapy resulted in a significantly higher bone mineral density (BMD), more trabecular bone, and higher strength when compared to radiotherapy alone [29,30]. Adding ZA to the radiotherapy treatment could even restore bone quality to those of healthy controls [29,30]. Krempien et al. [31] demonstrated that starting CL 3–6 days before radiotherapy resulted in a BMD and fractional trabecular volume similar to healthy bone, whereas not using CL or starting CL simultaneously with radiotherapy resulted in a bone quality which was lower than that of healthy bone. Both studies by Arrington et al. [29,30] showed that treating bone lesions with radiotherapy only resulted in a fractional trabecular volume and bone strength similar to metastatic bone that received no treatment at all.

Correlations between changes in bone mineral density, bone micro-architecture and strength were not reported in the included animal studies.

Patient studies

Effect of radiotherapy
Radiologic response. Six studies evaluated any qualitative radiologic response following radiotherapy [33,40,42,48,51,52,66] (Supplementary File D, 5th column). The definitions of radiological response used in these studies varied widely (Supplementary File B, 8–9th columns); a response not necessarily implicated that re-calcification occurred. Garmatis et al. [40] showed that immediately after radiotherapy (20–25 Gy in 8–10 fractions) almost 80% of the lesions show a marked improvement. This is in contrast with the trial (10 × 3 Gy vs. 3 × 5 Gy) by Rasmusson et al. [48] who found that, in similarly located bone lesions, at 1 month after radiotherapy about 60% of the lesions had not changed compared to their pre-radiotherapy status. However, at 3 months following radiotherapy the majority of the patients showed a complete or partial response (Supplementary File B). In addition, after 3 months the largest part of the improvements had already occurred. In other

studies [42,51,52,66], response rates ranged from 25% to 76%. It was unclear at what moment in time the data was provided for.

Bone density. Changes in bone density were investigated in seven studies [17,36–39,47,65] (Supplementary File D, 6th column). All studies showed the same trend: the bone density increased after radiotherapy. Foerster et al. [39] showed in a retrospective study that, in contrast to spinal bone metastases, the bone density in unaffected neighboring vertebral bodies did not change after radiotherapy. Three studies studied the bone density immediately after radiotherapy [17,37,65]. Whereas the clinically controlled trial by Koswig and Budach [17] showed that the bone density dropped by 8% (1 × 8 Gy) and 25% (3 × 10 Gy) immediately after radiotherapy, Wachenfeld et al. [65] (18 × 2 Gy) and Crone-Munzebrock et al. [37] (40–50 Gy in fractions of 2.5 Gy) did not find this initial drop. Two trials and one cohort study compared single-fraction radiotherapy with multiple-fraction radiotherapy [17,36,38]. Koswig et al. [17] and El-Shenshawy et al. [38] both demonstrated a significant increase in bone density after multiple-fraction radiotherapy compared to single-fraction radiotherapy after 6 months (mean: 1 × 8 Gy: 120% vs. 10 × 3 Gy: 173%, $p < 0.001$) and 3 months (post/pre ratio: 1 × 8 Gy: 1.05 vs. 5 × 4 Gy: 1.28 or 10 × 3 Gy: 1.81, $p = 0.049$), respectively. These results were not confirmed by the prospective cohort study by Chow et al. [36], which did not find a significant difference in density change between 1 × 8 Gy, 5 × 4 Gy, and 10 × 3 Gy (post/pre ratio: 1.28 vs. 1.41 vs. 1.45, $p = 0.26$) at 3 months after radiotherapy. McDonald et al. [47] distinguished between lytic and sclerotic lesions. The study showed that bone density in lytic metastases tended to increase, whereas sclerotic lesions tended to demineralize.

Pathological fractures. Eighteen clinical studies reported on fracture rate during follow up after radiotherapy [33–35,38,41,45,46,49,50,53–59,61,62] (Supplementary File D, 7th column). Overall, fracture rates after primary radiotherapy ranged from 0% to about 15%. In addition, reported rates on progression of spinal fractures after radiotherapy range from about 7% to 55% [50,58]. Three controlled clinical trials compared single-fraction radiotherapy with multiple-fraction radiotherapy (1 × 8 Gy vs. 10 × 3 Gy [41]; 1 × 8 Gy vs. 5 × 4 Gy or 10 × 3 Gy [38]; 1 × 8 Gy vs. 6 × 4 Gy [57]). While two of these studies observed more pathological fractures after single-fraction radiotherapy than after multi-fraction radiotherapy (6% vs. 2%, $p = 0.046$ [38]; 4% vs. 2%, $p = <0.05$ [57]), one study did not find a difference in pathological fracture rate (5% vs. 4%, p = not stated [41]). Studies on stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery (SRS) reported fracture rates ranging from approximately 2.5% to 32.5% [33,34,46,55,56,61,62]. In a retrospective matched-pair study, Sohn et al. [56] found two pathological fractures in patients who received SRS and no fractures in patients who received conventional radiotherapy.

Bone density and pathological fractures. The study by El-Shenshawy et al. [38] was the only study that assessed both bone density and fracture rate. A correlation was found between the range of bone density before and three months after radiotherapy and pathological fractures. The density change (ratio of median post/pre radiotherapy) of patients with a pathological fracture was lower, i.e. 0.78 (range 0.76–0.89) than those of patients without a pathological fracture (ratio 1.52 (range 0.67–3.42), $p = 0.001$).

Effect of radiotherapy combined with bisphosphonates

Six studies addressed the effect of adding BP to radiotherapy on bone quality [32,43,44,60,63,64] (Supplementary File E). Two retrospective cohort studies [43,60] compared changes in bone quality between patients receiving only radiotherapy and patients

receiving radiotherapy and BPs (ZA). The other four studies comprised a single patient group, which received both radiotherapy and BPs.

Radiologic response. The retrospective cohort study by Kijima et al. [43] showed that the response rate at 6–9 months after radiotherapy was significantly higher in patients receiving both radiotherapy and zoledronic acid compared to those receiving only radiotherapy (6/10 vs. 1/13, $p = 0.019$). It must be noted that the point of starting ZA varied from immediately after radiotherapy to 12 months after radiotherapy.

Bone density. Four studies focused on quantitative bone density [39,44,63,64] (Supplementary File E, 6th column). Of these, three studies consisted of a single intervention group. Although assessed using different methods, all three studies showed an increase in bone density over time after treatment with radiotherapy and disodium pamidronate (DP) or ibandronate (IB). Overall, from 3 months onward the bone density was significantly higher than its pre-radiotherapy value. Vassiliou et al. [64] distinguished between lytic, mixed and sclerotic lesions. Lytic metastases showed the largest changes in bone density, sclerotic lesions the least. Foerster et al. [39] performed a subgroup analysis on patients receiving radiotherapy combined with bisphosphonates versus patients receiving radiotherapy only. In both groups bone density increased over time. In addition, they found that the mean increase in bone density of metastases after 3 months was higher, albeit not significant, in patients receiving radiotherapy and bisphosphonates compared to patients receiving radiotherapy only (152.59 HU ± 141.99 vs. 76.03 HU ± 86.6, $p = 0.069$). After 6 months this effect was less profound (245.8 HU ± 151.5 vs. 171.9 HU ± 114.4, $p = 0.162$).

Pathological fractures. Five studies reported on pathological fractures during follow up [32,43,60,63,64] (Supplementary File E, 7th column). Of these, two studies, which were retrospective cohort studies, compared patients treated with radiotherapy with patients treated with radiotherapy and BPs. The first study reported one fracture in the former treatment group and no fractures in the latter group (p not stated) [43]. The second study found three fractures in patients treated with radiotherapy, and two fractures in patients treated with additional BPs (p not stated) [60]. Also, three additional patients (25%) treated with only radiotherapy underwent surgery for impending fractures. Furthermore, one randomized controlled clinical trial investigated the effect of high (10 × 3 Gy) and low (5 × 3 Gy) radiotherapy doses when combined with ZA [32]. Fractures were observed in both the high dose group and in the low dose group (4 vs. 3, p not stated).

Radiologic response and pathological fractures. The study by Kijima et al. [43] was the only study that assessed both radiologic response and fracture rate. However, correlations between radiological response and fracture rate were not reported.

Effect of radiotherapy combined with RANKL inhibitors

None of the included studies addressed the effect of radiotherapy combined with RANKL inhibitors on bone density, bone microarchitecture, bone strength or related outcome parameters.

Discussion

We conducted this study to systematically review all studies on the effect of (1) radiotherapy, (2) radiotherapy combined with bisphosphonates, and (3) radiotherapy combined with RANKL

inhibitors on bone quality and bone strength parameters in bone metastases originating from solid tumors.

In clinical practice, patients are often treated with a combination of local radiotherapy and systemic treatments. These systemic treatments include e.g. anticancer treatments with chemotherapy or hormonal therapy, BPs, and RANKL inhibitors. In this systematic review we only focused on BPs and RANKL inhibitors as treatments additional to radiotherapy, as these treatments intend to improve the bone mass. In contrast, other anticancer treatments are primarily used to attack tumor tissue and decrease lesion size. Future research needs to show whether other anticancer therapies have a secondary effect on bone quality and bone strength.

Animal studies were included in this review. Although the translation from pre clinical animal models to clinical practice is not straightforward, animal studies do have some benefits. Firstly, the experimental designs of animal studies can be very strictly regulated. Moreover, a negative control group (no treatment) can be formulated, which is not always possible in a clinical setting. A negative control enables one to assess the actual effect of e.g. radiotherapy. In addition, outcome measures of interest can be measured directly and more invasive measurements can be conducted. While bone strength in clinical studies needs to be measured indirectly via for example the number of pathological fractures, bone strength in animals can be determined by mechanically loading the bone until failure.

The three included animal studies showed that radiotherapy alone did not foster more new bone formation to restore microarchitecture or biomechanical strength than a negative control. In addition, treatment with radiotherapy did not restore bone quality and strength to the levels of healthy bones. However, BPs as an adjunct to radiotherapy seemed to be capable of significantly improving trabecular micro-architecture and restoring biomechanical strength to that of normal bone. Thus, based on the identified animal studies there was no evidence that radiotherapy alone leads to re-calcification or an increase in bone strength. It should, however, be noted that only two out of three animal studies determined bone strength and both studies were performed by the same research group. Also, one could argue that a time interval of 9 and 12 weeks is rather early for evaluating ossification. Further research is needed to address these issues.

All studies on the effect of radiotherapy on bone density showed the same trend: bone density increased after radiotherapy. However, there was insufficient evidence to conclude whether or not radiotherapy leads to an improved bone quality and increased bone strength in patients suffering from solid bone metastases. To assess whether radiotherapy indeed improves bone quality and bone strength, radiotherapy treatment should be compared to a negative control. In practice it is, however, difficult to perform studies with a negative control: not treating patients suffering from painful bone metastases might be ethically challenging. A good alternative for formulating a negative control group is comparing different treatment doses of radiotherapy in a randomized controlled trial. Van der Linden et al. evaluated the influence of different treatment schedules on the occurrence of a femoral fracture in 102 patients who participated in a randomized trial on the effectiveness of single-fraction vs multiple-fraction radiotherapy on pain [67]. The median time to fracturing from the start of radiotherapy was 6 weeks (range 2–29) for patients who received single-fraction radiotherapy (1 × 8 Gy) compared to median 17 weeks (range 2–35) for the multi-fraction (6 × 4 Gy) patients. Therefore, it was suggested that multi-fraction radiotherapy postponed the occurrence of a pathological fracture in patients with femoral metastases. Based on this finding it can be hypothesized that a higher dose of radiotherapy results in more re-calcification and thus to an improved bone strength than a lower dose of radiotherapy. The current systematic review identified three trials

comparing single-fraction radiotherapy with multiple-fraction radiotherapy. The conclusions on differences in fracture rates between single- and multiple-fraction radiotherapy varied between these studies. Previously, two meta-analyses of randomized studies comparing single-fraction versus multi-fraction radiotherapy for prevention of bone complications in patients with painful bone metastases were performed. The meta-analysis by Sze et al. [15] reported a higher pathological fracture rate after single-fraction radiotherapy (3.0%; 37/1240) than after multi-fraction radiotherapy (1.6%; 20/1236) (OR 1.82; 95% CI 1.06–3.11, $p < 0.05$). This difference was not found in the meta-analysis of Chow and colleagues: 3.2% (65/2018) of the patients developed a pathological fracture in the irradiated region after single-fraction versus 2.8% (57/2004) after multi-fraction radiotherapy (OR 1.10; 95% CI 0.61–1.99, $p = 0.75$) [12]. Thus, both the meta-analyses and our study are inconclusive on whether or not multi-fraction radiotherapy is associated with a lower pathological fracture rate than single fraction radiotherapy.

However, the results concerning the studies on fracture rate need to be interpreted with caution. Firstly, most studies were not designed to measure the fracture rate, but studied the effect of radiotherapy on the pain response. Fractures were 'only' noted during follow-up. Intensity and duration of follow-up were very heterogeneous among the several patient studies. The follow-up should be standardized when fracture rates are compared. A longer survival is accompanied with a higher risk of progression of disease and thus with a higher risk of fracture. To the best of our knowledge, there are currently no studies on the effect of radiotherapy dose with fracture rate as the primary outcome measure.

Furthermore, previous research on metastatic femora has shown that axial cortical involvement of the metastatic lesion was the only lesional parameter that was significantly predictive for fracturing [67]. A larger lesion implied a higher risk of fracture. Although more fractures occurred after a single dose of 8 Gy compared to 6 fractions of 4 Gy (23% vs. 7%, $p = 0.02$), Van der Linden et al. did not find the treatment schedule to be predictive for fracturing when correcting for the axial cortical involvement ($p = 0.07$) [67]. Thus, lesion size might be more important than the radiotherapy dose in predicting fracture risk. The studies comparing the effect of single-fraction and multi-fraction radiotherapy on fracture rate included in this systematic review did not correct for lesions size.

In addition, the preexistence of fractures or impending fractures should be taken into account. The exclusion criteria concerning these factors varied across studies included in this systematic review.

When considering changes in bone density, all studies showed the same trend: bone density seemed to increase after treatment with radiotherapy. However, as these studies lacked a control group (no treatment), it cannot be concluded that the increase in bone density was due to the radiotherapy. In addition, co-medication, including BPs, was allowed in most studies. As BPs are known to increase bone density, the observed increase in bone density could also be caused by the BPs. Again, it must be stressed that in practice it is challenging to perform patient studies fulfilling these criteria.

There were discrepancies in the results of papers studying the effect of single-fraction radiotherapy compared with multiple-fraction radiotherapy on bone density. While the studies by Koswig et al. and El-Shenshawy et al. found a higher increase in bone density after multiple-fraction radiotherapy than after single-fraction radiotherapy, Chow et al. did not confirm these findings. In the latter study patients received either 1×8 Gy, 5×4 Gy, or 10×3 Gy and were analyzed as three different groups. In the study by El-Shenshawy et al. patients also received 1×8 Gy, 5×4 Gy, or 10×3 Gy, but patients receiving multiple fractions were analyzed as a single group. In order to draw conclusions, studies should be analyzed in a similar way.

Unfortunately, no correlations between changes in bone density, bone micro-architecture, and bone strength were reported in the animal studies and barely in the patient studies. Therefore, direct correlations between fracture rate and bone density could not be made on an animal-to-animal or patient-to-patient basis. Bone fragility is influenced by bone mass, bone micro-architecture, and tissue quality [68]. An increase in bone mass, i.e. bone density, does not necessarily mean that this newly created bone results in increased bone strength. Thus, fractures can still occur. Without correlating changes in bone mass and fracture rate, no conclusions can be drawn on whether it is the process of re-calcification that leads to improved bone strength or not. Future studies should, therefore, determine both bone quality and bone strength or fracture rate within the same animal or patient.

The combination of BPs and radiotherapy showed an increase in bone density in metastatic bone lesions in all included studies. However, the number and quality of studies that actually compared radiotherapy + BP treatment with radiotherapy treatment was limited. Although the included patient studies that compared radiotherapy + BP treatment with radiotherapy seem to show a positive effect of adjunct BPs on bone quality, this was not significantly different [39,43,60]. Therefore, there was insufficient evidence to draw any firm conclusions on the additional effect of BPs. Several animal studies, however, showed positive effects of BP as adjunct therapy in increasing bone stability [29,30]. Although challenging, we therefore recommend performing randomized patient studies of good methodological quality to investigate the adjunct effect of BPs. Recently, Hoskin et al. evaluated the effect of ibandronate vs single-fraction radiotherapy (1×8 Gy) on the occurrence of a pathological fracture in 470 patients participating in a randomized controlled trial focusing on pain [69]. They did not find a statistical difference in the occurrence of a pathological fracture (ibandronate: 7 (3%) vs. radiotherapy: 5 (2%), $p = 0.31$), suggesting equal effectiveness of ibandronate and radiotherapy on improving bone strength.

Similarly, this systematic review showed that neither animal nor patient studies have been performed on the effect of radiotherapy combined with RANKL inhibitors on bone quality and bone strength. Recent studies showed that RANKL inhibitors, i.e. Denosumab, are more effective in preventing skeletal related events than bisphosphonates [70–72]. Therefore, it would be valuable to investigate the possible additive effect of RANKL inhibitors with radiotherapy over BPs with radiotherapy. Animal studies might be suitable to provide a first estimation on this effect.

Although this review provides an overview of the effects of radiotherapy, BPs and RANKL inhibitors in a systematic manner, there are several limitations to consider. Firstly, the majority of included studies lack a control group. Therefore, the effects found in these studies could not be attributed with certainty to the treatment given. Randomized controlled trials are needed to establish whether radiotherapy alone increases bone stability and whether BPs or RANKL inhibitors have an additive effect on improving bone quality and bone strength.

In addition, there was a lot of variation between studies in terms of measuring the radiological response and bone density. In the eight studies reporting on radiologic response seven unique definitions were used for radiologic response; in eight studies reporting on bone density three different methods were used. The use of different methods and definitions complicates comparison of results between studies. Therefore, it would be beneficial if such outcome measures would be standardized, as has been done for pain scores.

Moreover, as stated above, most patient studies were not designed to measure fracture rates, but studied the pain response

after radiotherapy. Fractures were noted during follow-up. To be able to assess the actual effect of radiotherapy on fracture risk, studies should be designed with fracture rate as the primary outcome measure. In addition, all factors affecting the fracture risk, such as lesion size, preexisting or impending fractures, and perhaps also the load applied to the skeleton during physical activities, should be taken into account in the study design.

The final point of concern is the quality of the included papers. Only four studies were evaluated as 'strong'. Of these, one is an animal study [30], two are controlled clinical trials comparing the effect of multi- versus multiple-fraction radiotherapy [41,57], and one is cohort study investigating the changes in bone density after radiotherapy + BP treatment [63]. When focusing on the good quality papers only, still no firm conclusions on the effect of radiotherapy, BPs and RANKL inhibitors on bone quality and bone strength can be drawn, as (1) the controlled clinical trials were not designed to measure fracture rate, (2) the results of the controlled clinical trials are inconclusive and (3) the only study on BPs lacks a control group.

Although the clinical experience of many clinicians is that radiotherapy strengthens bones due to re-calcification in a large proportion of patients, this is not supported by this systematic review. This discrepancy may be explained by the fact that our literature search identified no large prospective, controlled patient studies primarily looking at re-calcification or fracture rate. Also, the studies that were included in this review employed different definitions of similar outcome measures and used different methods to quantify them. This might have resulted in the inability to identify changes in bone quality and fracture rate after radiotherapy. However, it could also be questioned whether the changes seen on X-rays or CT images indeed reflect the appearance of newly formed bone that is of sufficient quality to improved bone strength.

In this systematic review we obtained a biomechanical approach and focused on changes in bone density and pathological fractures. In clinical practice, however, radiotherapy may not only be administered to prevent pathological fractures, but also for metastatic cord compression (MSCC) and pain. Previous studies have shown that the addition of zoledronic acid to radiotherapy improved local control and overall control of MSCC in patients irradiated for this complication in bone metastases [73]. In addition, a study showed that more vertebrae were stable after radiotherapy than before treatment [54]. Therefore, in order to fully evaluate the effectiveness of radiotherapy, with or without bisphosphonates or RANKL inhibitors, a broad spectrum of outcome parameters should be considered. Based on our systematic review, however, we only conclude that there is a lack of evidence that radiotherapy, with or without bisphosphonates or RANKL inhibitors, increases bone density and prevents pathological fractures.

Conclusion

Based on this systematic review, it can be concluded there was no sufficient evidence that radiotherapy had a positive effect on bone quality and fracture risk. In addition, animal studies showed that the addition of BPs to radiotherapy restored bone quality and bone strength to that of healthy bone, whereas this is not yet proven in patients. Furthermore, there were neither animal nor patient studies addressing the effect of RANKL inhibitors as an adjunct to radiotherapy on bone quality and bone strength.

Author contributions

All authors have made substantial contributions to all three of the following sections:

1) The conception and design of the study, or acquisition of data, or analysis and interpretation of data;
2) Drafting the article or revising it critically for important intellectual content; and
3) Final approval of the version to be submitted.

Conflicts of interest statement

No conflict of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2016.03.001.

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