Review Article

Effect of Bisphosphonates on Skeletal Related Events in Long Bone Metastases of Renal Cell Carcinoma: A Systematic Review

Danique LM van Broekhoven,[1] Lisa W Dootjes,[1] Astrid van der Veldt,[2] Carola Zillikens,[3] Jakob van Oldenrijk[1]

Abstract

Bone metastases (BMs) in patients with renal cell carcinoma (RCC) are lytic lesions which are prone to skeletal related events (SREs) such as (pending) pathological fractures or bone pain requiring radiotherapy or surgery. The aim of this review is to assess whether the use of bisphosphonates in patients with RCC and BMs in the long bones results in reduced SRE rate. A systematic review of literature was conducted, using PubMed, Embase, Medline, Web of Science, Cochrane, and Google Scholar (date 1971 till June 2021). All clinical studies on bisphosphonates in patients with RCC and BMs in long bones were retrieved. Primary outcome measure was SRE rate of BMs in long bones. Secondary outcome was fracture rate of BMs in long bones. Fourteen relevant articles were selected. Bisphosphonates reduced the mean skeletal morbidity rate by 0.4-0.95 SREs/year and had a pooled SRE rate of 38.3% (95% confidence interval [CI] 28.4%-49.3%). When bisphosphonates were added to radiotherapy the pooled SRE rate was 18.4% (95% CI, 10.5%-30.3%). In addition, pooled effect sizes showed a significant SRE risk reduction (RR 0.45, 95% CI, 0.24-0.85) in the bisphosphonates combined with radiotherapy group. There was limited reported data on rate of pathological fractures. In general, bisphosphonates reduce the SRE rate in RCC patients with BMs. The level of evidence for the effect of bisphosphonates on the rate of pathological fractures in patients with long BMs of RCC is low.

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Introduction

Renal cell carcinoma (RCC) accounts for approximately 2% of all malignancies with an increasing incidence.[1] At diagnosis, about one-third of patients already have bone metastases (BMs) and another third of patients will develop BMs during the course of the disease.[2-4] The overall survival of patients with metastatic RCC has improved significantly since the introduction of targeted therapy, immunotherapy and combinations of these therapies, increasing from 1 year to a median survival up to 4 years.[1,5-7] Since more patients with metastatic RCC have a longer survival, the incidence of BMs in these patients is rising.

In patients with RCC, BMs have a significant impact on quality of life since these lytic lesions are prone to skeletal related events (SREs), which are defined as pathological fractures, surgery to bone for pending pathological fractures, bone pain requiring radiotherapy, spinal cord and nerve root compression, and hypercalcaemia. SREs are experienced by approximately 80% of patients with RCC and BMs resulting in severe pain, high morbidity, and poor quality of life in the palliative phase.[2,4,8] In particular, BMs of the long bones present a challenge. These lesions have a high risk of fracturing due to weight bearing and forces acting on the bone during movement. Impending fractures or actual fractures of long BMs often require invasive surgical stabilization.

Bisphosphonates are highly effective inhibitors of osteoclast-mediated bone resorption[9] and have shown considerable effect in lowering the SRE rate in patients with breast cancer, multiple myeloma, and solid tumors.

Literature on the use of bisphosphonates for BMs in patients with RCC suggests the same beneficial effect, though it is not yet common practice.[10] However, knowledge of the effect of bisphosphonates on the SRE rate in patients with RCC and BMs in long bones is limited.

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Table 1 Complete Search

Embase 63
('bone metastasis'/de OR (('bone cancer'/de OR 'bone tumor'/exp OR 'femur'/de OR 'tibia'/exp OR 'fibula'/exp OR 'ulna'/exp OR 'radius'/exp OR 'humerus'/exp OR 'bone pain'/de OR 'skeleton'/de) AND ('metastasis'/de)) OR (((femur* OR tibia* OR fibul* OR ulna* OR radius OR radial* OR humerus* OR bone* OR osseous* OR osteoblastic* OR osteoclastic* OR osteoplastic* OR skelet*) NEAR/6 (metas*))):ab,ti,kw) *AND* ('bisphosphonic acid derivative'/exp OR (bisphosphon* OR biphosphon* OR diphosphon*):ab,ti,kw) *AND* ('fracture'/exp OR (fractur*):ab,ti,kw) *AND* ('renal cell carcinoma'/de OR (((renal OR kidney OR nephr*) NEAR/3 (cell) NEAR/3 (cancer* OR tumor* OR tumour* OR carcin* OR neoplas*))):ab,ti,kw) *NOT* ([Conference Abstract]/lim)
Medline Ovid 1
((("Bone Neoplasms"/ OR exp "Femur"/ OR "Tibia"/ OR "Fibula"/ OR "Ulna"/ OR "Radius"/ OR "Humerus"/ OR "Skeleton"/) AND (exp "Neoplasm Metastasis"/)) OR (((femur* OR tibia* OR fibul* OR ulna* OR radius OR radial* OR humerus* OR bone* OR osseous* OR osteoblastic* OR osteoclastic* OR osteoplastic* OR skelet*) ADJ6 (metas*))).ab,ti,kf.) *AND* ((biphosphon* OR diphosphon*).ab,ti,kf.) *AND* (exp "Fractures, Bone"/ OR (fractur*).ab,ti,kf.) *NOT* (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. *AND* ("Carcinoma, Renal Cell"/ OR (((renal OR kidney OR nephr*) ADJ3 (cell) ADJ3 (cancer* OR tumor* OR tumour* OR carcin* OR neoplas*))).ab,ti,kf.)
Web of Science 1
TS=(((((femur* OR tibia* OR fibul* OR ulna* OR radius OR radial* OR humerus* OR bone* OR osseous* OR osteoblastic* OR osteoclastic* OR osteoplastic* OR skelet*) NEAR/5 (metas*)))) *AND* ((biphosphon* OR diphosphon*)) *AND* ((fractur*)) *AND* (((renal OR kidney OR nephr*) NEAR/2 (cell) NEAR/2 (cancer* OR tumor* OR tumour* OR carcin* OR neoplas*)))) *AND* DT=(Article OR Review OR Letter OR Early Access)
Cochrane 2
((((femur* OR tibia* OR fibul* OR ulna* OR radius OR radial* OR humerus* OR bone* OR osseous* OR osteoblastic* OR osteoclastic* OR osteoplastic* OR skelet*) NEAR/6 (metas*))):ab,ti,kw) *AND* ((biphosphon* OR diphosphon*):ab,ti,kw) *AND* ((fractur*):ab,ti,kw) *AND* ((((renal OR kidney OR nephr*) NEAR/3 (cell) NEAR/3 (cancer* OR tumor* OR tumour* OR carcin* OR neoplas*))):ab,ti,kw)
Google Scholar 200
Bisphosphonic|bisphosphonate|bisphosphonates 'bone metastasis'|femur|tibia|fibul|ulna|radius|radial|humerus|osseous|osteoblastic|osteoclastic| osteoplastic metastasis|metastatic| fracture|fractures "renal|kidney cell cancer|tumor|tumour|carcinoma|neoplasm
Other source 8
References included articles

The aim of this systematic review was to assess whether the use of bisphosphonates in patients with RCC and BMs in the long bones results in a reduced SRE rate overall and fracture rate as secondary outcome.

Patients and Methods

Search Strategy and Eligibility Criteria

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were used for performing this systematic review.[11] A systematic review of the literature was conducted to retrieve all clinical studies, including randomized control trials, cohort and case series, listed in PubMed, Embase, Medline, Web of Science, Cochrane, and Google Scholar (date 1971 till June 2021) containing information on bisphosphonate use and SREs of long BMs in patients with RCC.

The search was performed on December 4, 2020 and updated on June 1, 2021. The search strategy is shown in Table 1. All retrieved titles were combined in Endnote X9 Clarivate Analytics, duplicate articles were removed and all titles and abstracts were independently screened by 2 authors to select eligible articles (DvB and ED). Full-text of all eligible articles were read and included or excluded for the review based on the criteria given in Table 2. Any discrepancy between authors was resolved through discussion. Cross-reference of all included full-text articles was used to identify relevant articles that had not been found through the literature search.

Analysis of Data

Primary outcome measure was SRE rate of long BMs. Secondary outcome was fracture rate of long BMs. The Methodological Index for Non-Randomized Studies (MINORS) was used to assess risk of bias.[12] Two assessors (DvB and ED) reviewed all included articles independently. Any discrepancy between the assessors was resolved through discussion.

A meta-analysis was performed using R statistical software (version 4.1.0) with meta for package. Mean skeletal morbidity rate were calculated based on the data of the included studies. In addition, pooled SRE rates were computed between comparable study groups. The meta-analysis was performed on selected studies, using a fixed-effect model (Mantel-Haenszel method) if P-value $>$ .1 and $I^2 < 50\%$.

Results

Literature Search

The search process of this systematic review is presented in the PRISMA flow chart (Figure 1). The initial search identified 260 studies and 18 articles were selected for full text analysis. The references of these 18 articles were checked and an additional 8 studies were screened based on title and abstract. This led to inclusion of 4 more articles for full text analysis. After reading the full text of these 22 articles, 9 were excluded: 5 articles did not describe a clinical study, 3 articles did not stratify for RCC and 1 did not reported SRE or fracture rate. Finally, 13 articles met all inclusion criteria.[4,13-24] The MINORS score ranged from 3 to 15 (Table 3).

Details on patient characteristics, BM characteristics (such as size) and previous treatment lines were not reported in most studies. When available, details are presented below.

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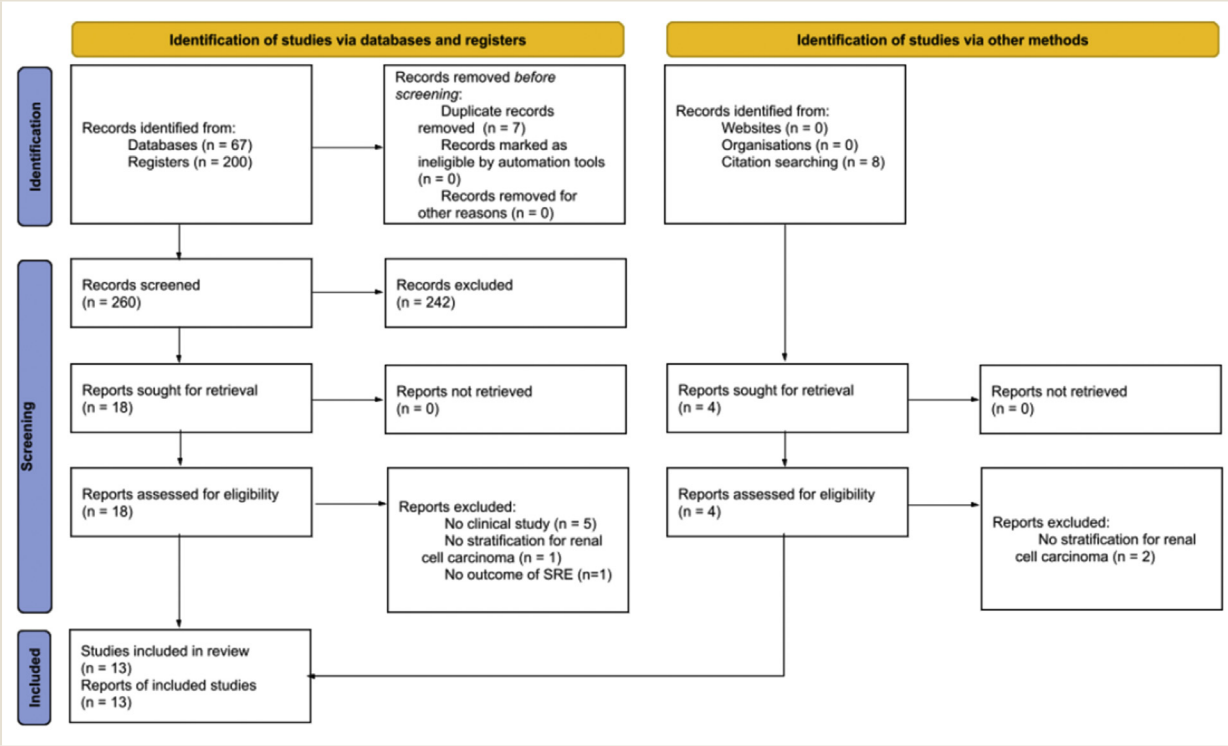
Table 2 Inclusion and Exclusion Criteria

Inclusion	Exclusion
Long bone metastases of renal cell carcinoma	Case reports
Treatment with bisphosphonates	Spinal metastases
Results including risk of fracture	No stratification for tumor type
Clinical study	
Original publications in English or Dutch language	

Figure 1 PRISMA flowchart.



Primary Outcome Measures

The outcome measures are summarized for each study in Table 3. Eight studies had SRE as primary outcome, 2 studies as secondary outcome measure. In all studies, SRE was defined as pathologic fracture, spinal cord compression, severe pain or surgery or radiotherapy for local recurrence. Two studies used a modified definition of SRE; Woodward et al[4] added hypercalcaemia as SRE, and Smidt-Hansen et al[21] evaluated disease progression instead of surgery or radiotherapy.

Bisphosphonates reduced the mean skeletal morbidity rate (SMR), defined as the number of SREs per person-year at risk, by 0.4-0.95 SREs/year[4,13,14,20] and had a pooled SRE rate of 38.3% (95% confidence interval [CI] 28.4%-49.3%), in studies with a placebo group[13,14] and pooled SRE rate of 45.2% (95% CI, 26.5%-65.4%), in studies without a control group.[15,17,19,21] When bisphosphonates were added to radiotherapy the pooled SRE rate was 18.4% (95% CI, 10.5%-30.3%).[16,18,23] Details on these results are listed below. Results are presented as reported in the original articles, details on relative risk or 95% confidence intervals were not available.

Bisphosphonate Therapy

In total, 9 studies either compared the effect of bisphosphonate therapy to placebo or no bisphosphonate therapy[4,13,14,19-22] or investigated the combination of bisphosphonate therapy with different specific targeted therapy strategies.[15,17] Patients in all these studies continued targeted treatment for RCC, but details on current or previous regimes were not reported. Of these 9 studies, 6 reported a reduction of the SRE rate when treated with bisphosphonate therapy. Three studies reported no clinical benefits of bisphosphonates to the SRE rate.

Lipton et al[13] conducted a retrospective subset analysis in the patients with RCC from a phase III, double-blind, randomized controlled trial comparing zoledronate with placebo in patients with

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Table 3 Outcome Measures of Included Articles

Author, Year	Study Design	Patients With mRCC (n)	Location Bone M'etastasis (n)	Therapy (n)	Control (n)	Primary Outcome	MINORS Score
Lipton et al[13] 2003	Subset analysis[a]	74	Not specified	Zoledronate (27)	Placebo (19)	SRE	8
Saad et al[14] 2005	Subset analysis[a]	46	Not specified	Zoledronate (27)	Placebo (19)	SRE	11
Woodward et al[4] 2011	Retrospective cohort	254	Not specified	Bisphosphonate therapy (81)	No bisphosphonate therapy (173)	SRE rate	3
Yasuda et al[20] 2012	Retrospective cohort	45	Not specified	Zoledronate (23)	No zoledronate (22)	SRE rate[b]	8
Tunn et al[19] 2012	Prospective phase IV trial	49	Not specified	Zoledronate (49)	No	SRE	9
Smidt-Hansen et al[21] 2013	Retrospective cohort	30	Not specified	Zoledronate (30)	No	SRE	10
McKay et al[22] 2014	Post hoc analysis[c]	781	Not specified	Bisphosphonate therapy (162)	No bisphosphonate therapy (619)	Progression-free survival	10
Tannir et al[15] 2006	Pilot trial	15	Not specified	Zoledronate + thalidomide + IFN-γ (15)	No	Time to SRE	8
Manoukian et al[17] 2011	Pilot trial	11	Not specified	Zoledronate + statin (11)	No	Time to SRE	11
Kijima et al[16] 2009	Retrospective cohort	23	Not specified	Radiotherapy + zoledronate (10)	Radiotherapy monotherapy (13)	SRE[b]	15
Takeda et al[18] 2012	Retrospective cohort	27	Spine (15) Femur, tibia (5) Other (14)	Radiotherapy + zoledronate (16)	Radiotherapy monotherapy (18)	Time to SRE	15
Hosaka et al[23] 2018	Retrospective cohort	62	Spine (34) Pelvis (14) Extremities (10) Others (4)	Radiotherapy + zoledronate (35)	Radiotherapy monotherapy (27)	Postirradiation SRE, postirradiaton SRE free rate	13
Harada et al[24] 2021	Prospective cohort	27	Spine (18) Extremities (5) Pelvic bone (4) Others (3)	Radiotherapy + zoledronate (27)	No	1-year local SRE free survival	14

Abbreviations: mRCC = metastatic renal cell carcinoma; SRE = skeletal related events.
*[a] Subset analysis of phase III, double-blind, randomized controlled trial.
**[b] Secondary endpoint.
***[c] Post hoc analysis of phase II and phase III trials.

BMs from solid tumors.[25] They included 46 patients with RCC and BMs, 27 patients were treated with zoledronate and the other 19 patients received placebo. Additional therapy was not reported. Follow up time in this study was 9 months. The percentage of patients who experienced an SRE was 37% in the zoledronate group and 74% in the placebo group ($P = .015$). Similarly, the mean SMR was reduced from 3.38 events/year in the placebo group to 2.68 events/year in the treatment group. In addition, the zoledronate group had a significant delay in the time to first SRE (median time was not reached in the zoledronate group vs. 72 days in the placebo group, $P = .006$). Finally, the time to first pathologic fracture was delayed significantly in the zoledronate group (median not reached vs. 168 days in the placebo group, $P = .003$). Patients treated with zoledronate had a significant risk reduction of 61% on the development of SREs compared with the placebo group ($P = .008$).

Saad et al [14] analyzed the same group of 46 patients with RCC and BMs as the study of Lipton et al 2003[13] with a longer follow up time of 12 months and found similar beneficial results. Patients treated with zoledronate still had a significant reduction of the incidence of SREs (41% vs. 79% in the placebo group, $P = .011$). The mean SMR was reduced from 3.13 events/year to 2.58 events/year in the placebo and treatment group, respectively. In addition, the onset of SREs as well as the time to first pathologic fracture was delayed by almost 1 year when treated with zoledronate ($P = .007$ and $P = .003$, respectively). In patients with metastatic RCC, the risk decreased significantly by 58% compared with placebo.

The retrospective study of Woodward et al[4] included 254 patients with RCC and BMs of whom 81 patients received bisphosphonates. The other 173 patients were included in a historical control group. Additional systemic treatment was allowed. Bisphosphonates significantly improved the SMR (1.0 in the bisphosphonate group vs. 1.4 in the control group). In all 254 patients, 56 pathologic fractures (9.3% of all SREs) were reported, of which

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44 were in long bones. No specification was made regarding groups.

Yasuda et al[20] reported on a retrospective cohort, including 45 patients with RCC and BMs. Twenty-three patients received zoledronate whereas the other matched 22 patients did not. Concurrent immunotherapy and targeted therapy were allowed. Of the 10 patients receiving targeted therapy as the first line, 9 patients also received zoledronate. Patients in the zoledronate group experienced a lower SRE rate (0.87/year) compared to the control group (1.82/year) ($P = .048$). Pathologic fracture rate was not significantly reduced (0.05/year in the zoledronate group vs. 0.19/year in the control group, $P = .19$).

The prospective phase-IV trial of Tunn et al[19] included 49 patients who all received zoledronate, in addition to targeted therapy. Thirty-eight of the 49 patients (78%) experienced no SRE at 1-year follow-up. Seven of the total of 21 SREs (33.3%) were a pathologic fracture, not specified to location.

The retrospective cohort study of Smidt-Hansen et al[21] investigated 30 patients who all received zoledronate, in addition to targeted therapy or interleukin-2-based immunotherapy as first, second or third line treatment. The SRE-free rate for the whole cohort was 53%. Two patients (7%) developed a pathologic fracture. Follow up period was not described.

The study of McKay et al[22] showed the post-hoc analysis of 8 phase 2 and phase 3 studies, including a total of 718 patients with RCC and BMs of whom 162 received bisphosphonate therapy (zoledronate or pamidronate). The other 619 patients received no bisphosphonates. Additional targeted therapy was allowed. The SRE rate in patients receiving bisphosphonate therapy was 8.6% (14/162), compared to 5.8% (36/619) in patients not receiving bisphosphonate therapy ($P = .191$). 41 of all 50 SREs were pathologic fractures, not specified for both groups.

In the pilot trial of Tannir et al[15] 15 patients were treated with the combination of zoledronate, thalidomide and interferon-γ. Concurrent chemotherapy, radiotherapy, or surgery was not permitted. Thirteen of the 15 patients showed disease progression (87%), of whom 9 patients had an SRE. One SRE was a pathologic fracture.

Manoukian et al[17] performed a pilot trial in 11 patients, with RCC and BMs only, to assess the effect of zoledronate combined with a statin on the onset of SREs. Five patients received concurrent treatment with sunitinib and 1 patient with sorafenib and interferon during the study. SRE-free rate was 36% for the median time of follow up of 12 months. No pathologic fractures were reported.

Bisphosphonate Therapy Combined With Radiotherapy

In 4 studies, bisphosphonates were added to radiotherapy and compared to radiotherapy only. Patients in all these studies were continuing targeted treatment for RCC, details on regimes were not reported. All 4 studies reported clinical benefits of bisphosphonate therapy combined with radiotherapy compared to radiotherapy only.

The retrospective study of Kijima et al[16] investigated 10 patients with RCC and BMs treated with zoledronate combined with radiotherapy compared to 13 matched historical patients treated with radiotherapy only. The patients received no systemic therapy, except interferon alfa or interleukin 2. In the zoledronate combined with radiotherapy group, only 1 patient had an SRE (10%), which was not a pathologic fracture. By contrast, 10 patients in the radiotherapy group had SREs (77%) ($P = .003$). Of them, only 1 patient had a pathologic fracture (10%). In addition, zoledronate combined with radiotherapy prolonged the SRE-free survival time (median time not reached vs. 18.7 months in the radiotherapy group, $P = .046$).

Takeda et al[18] retrospectively analyzed 27 patients with a total of 34 BMs. Concomitant immunotherapy with interferon alfa was allowed. Fifteen patients were treated with zoledronate and radiotherapy, the other 12 patients received radiotherapy only. Three patients in the zoledronate combined with radiotherapy group had SREs (19%) compared to 6 patients (8 lesions) in the radiotherapy group (44%). Zoledronate significantly prolonged the time to SRE on the irradiated site ($P = .047$). Of the 3 patients with an SRE in the zoledronate combined with radiotherapy group 2 had a pathologic fracture of the femoral neck (67%), 3 lesions in the radiotherapy group were pathologic fractures (38%).

The retrospective study of Hosaka et al[23] investigated 62 patients, 35 in the zoledronate combined with radiotherapy group and 27 in the radiotherapy group. Thirty-four patients also received systemic treatment, sunitinib as the most commonly prescribed agent (22 in the combined group and 3 in the radiotherapy group). The SRE-free rate at 2 years was significantly higher in the zoledronate combined with radiotherapy group (73%) compared to the radiotherapy group (44%) ($P = .02$). However, the effect on the SRE-free rate in the zoledronate combined with radiotherapy group (n = 35) was enhanced by sunitinib as the SRE-free survival was significantly higher in patients who were treated with sunitinib (n = 22) than those who were not (n = 13) (respectively 92% and 53%, $P = .03$). Although the SRE-free rate in patients who were not administered sunitinib was slightly higher in the zoledronate combined with radiotherapy group, no significant difference between both groups was found ($P = .5$).

Harada et al[24] conducted a prospective cohort study of 27 patients who all received the combination of zoledronate and radiotherapy. No additional systemic treatment was allowed. The 1-year local SRE-free survival was 78%. One of the 6 SREs was a pathologic fracture in the humerus.

Meta-analysis

Pooled effect sizes showed a significant SRE risk reduction (RR 0.45, 95% CI, 0.24-0.85) in patients with RCC and BMs treated with bisphosphonates combined with radiotherapy compared to radiotherapy monotherapy (Figure 2).[16,18,23] The I^2 test showed no significant heterogeneity among the studies ($I^2 = 5.7\%$; $P = .35$).

Secondary Outcome Measures

Table 4 shows the total number of SREs and for each SRE separately. Almost all studies reported data on pathologic fractures, including by therapy group.

Bisphosphonates reduced the skeletal morbidity rate of pathologic fractures with 1.19-0.14 fractures/year[4,20] and the pathologic fracture rate with 66% (25%-100%).[13,16,18,23] Overall fracture rate in patients treated with bisphosphonate therapy ranged from 0% to 12.5%.[13,15-19,21,23,24] In addition, bisphosphonate therapy

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Table 4 Specified SRE Per Treatment Arm

Author, Y	Number of SREs (% of Patients)		Pathologic Fractures (Location)		Surgery to Bone		Radiotherapy		Spinal Cord Compression		Hypercalcaemia		Other
	Therapy	Control	Therapy	Control	Therapy	Control	Therapy	Control	Therapy	Control	Therapy	Control	
Lipton et al[13] 2003	20 (37)	35 (74)	4 (1 vertebral, 3 nonvertebral)	16 (5 vertebral, 11 nonvertebral)	3	4	11	12	2	3	-	-	
Saad et al[14] 2005	11 (41)	15 (79)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	-	
Woodward et al[4] 2011	604[a] (85)	-	56[a] (44 long bones, 8 vertebral, 4 other)	-	72[a]	-	368[a]	-	70[a]	-	38*	-	
Yasuda et al[20] 2012	0.87/y	1.82/y	0.05/y (n.s.)	0.19/y (n.s.)	0.17/y	0.47/y	0.64/y	0.91/y	0/y	0.13/y	-	-	
Tunn et al[19] 2012	11 (22)	-	7 (n.s.)	-	6	-	6	-	2	-	-	-	
Smidt-Hansen et al[21] 2013	14 (47)	-	2 (n.s.)	-	0	-	0	-	2	-	-	-	11 PD
Tannir et al[15] 2006	9 (60)	-	1 (rib)	-	0	-	6	-	0	-	-	-	1 RFA 1 Intrathecal pump
Manoukian et al[17] 2011	7 (64)	-	0	-	0	-	1	-	0	-	-	-	1 cryoablation 5 PD
McKay et al[22] 2014	14 (9)	36 (6)	41[a] (n.s.)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	-	
Kijima et al[16] 2009	1 (10)	10 (77)	0	1 (n.s.)	0	3	1	4	0	2	-	-	
Takeda et al[18] 2012	3 (19)	8 (44)	2 (femoral neck)	3 (n.s.)	0	3	0	1	0	1	-	-	
Hosaka et al[23] 2018	7 (20)	9 (33)	1 (n.s.)	2	0	1	3	6	3	0	-	-	
Harada et al[24] 2021	6 (22)	-	1 (humerus)	-	2	-	2	-	5	-	-	-	

Abbreviations: n.s. = not specified; PD = progressive disease; RFA = radiofrequency ablation; SRE = skeletal related events.
*[a] Data from the entire cohort, not specified for bisphosphonate therapy or control group.

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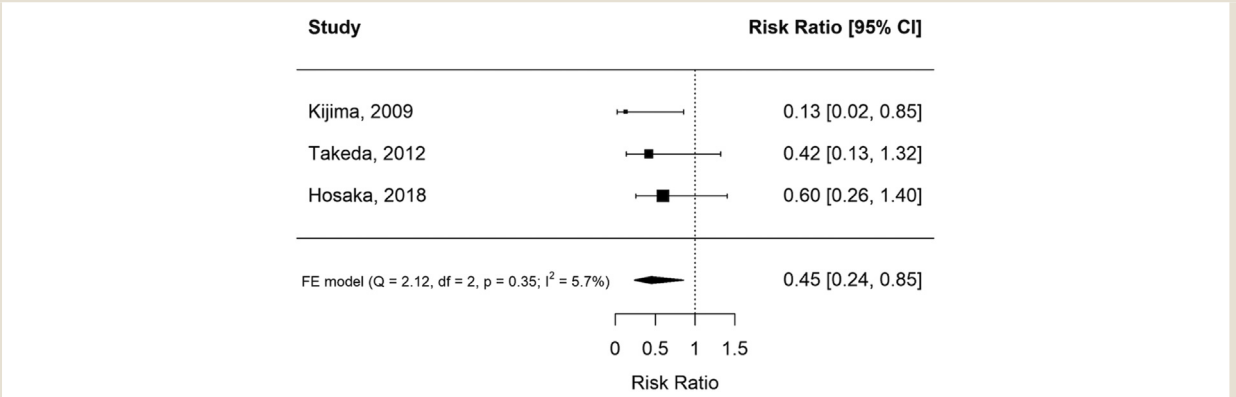
Figure 2 Forest plot of SRE risk in bisphosphonate treatment combined with radiotherapy.



delayed the time to onset of pathologic fractures by more than 6 months.[13,14]

Only 3 articles described the location of BMs at baseline[18,23,24] (Table 3) and in addition, pathologic fractures are not differentiated into long bone, vertebrae, or other locations in 8 studies.

Discussion

The use of bisphosphonates for BMs in cancer patients is increasing. Overall, in patients with RCC and BMs the SRE rate is 80% during the course of disease.[2-4] This systematic review describes evidence from numerous retrospective series and a few small prospective randomized studies supporting the hypothesis that bisphosphonates reduce de SRE rate of BMs in RCC patients. However, the overall quality and quantity of evidence in the published literature is not convincing. It is difficult to determine the effect of bisphosphonates on BMs from RCC because the present literature is limited about the timing of bisphosphonates, time to disease progression and follow-up time.

There were only 2 subset analyses available, both from the same randomized placebo-controlled trial. The only large study was a post-hoc analysis, which reported no statistical difference in SRE rate. Four observational trials reported an SRE rate varying between 11% and 64% after 1 year and 60% SRE in total for patients treated with bisphosphonates. All 5 of the comparative retrospective cohort studies showed a significant reduction of SRE rate with the administration of bisphosphonates. One retrospective case series reported a SRE free rate of 53%, no follow up specified. Due to the difficulty of comparing the included studies, our systematic review could only perform a meta-analysis of the radiotherapy subset.

When interpreting the MINORS score, there is a discrimination between comparative and non-comparative studies. MINORS is a validated instrument to assess the methodology quality of nonrandomized studies. The ideal score of 24 for comparative studies and 16 for non-comparative studies[12] was not obtained by any included study. The comparative studies had MINORS score ranging from 3 to 15, median 11.5, whereas the noncomparative studies had MINORS score ranging from 8 to 14, medial 10.

In this systematic review, limited information was found on pathologic fracture rate for long BMs. Due to the low numbers, no strong conclusions can be drawn in relation to bisphosphonates. The incidence of pathological fractures of BMs in patients with RCC is not well described. Most studies include pathological fractures in SREs but do not stratify the types of SRE in their results or discriminate for long bones. As such, it is hard to extract specific data. In addition, no distinction has been made in any study between new pathological fractures and fixation failures.

Patients with RCC receive targeted therapy and/or immunotherapy. Treatment regimens can differ, as well as interactions with bisphosphonates. Current literature does not clearly stipulate which treatment regimens patients undergo. As such, it is difficult to determine the effect of bisphosphonates on BMs.

The use of bisphosphonates as treatment for BMs was initiated around 1995.[26] Specific use for metastases in patients with RCC only followed after 2004[4] and was a relatively new indication for a known drug. Although current Dutch guidelines do not include the use of bisphosphonates in RCC, the threshold for the application in patients with RCC and BM is relatively low, indications include pain. Based on the short period of experience with bisphosphonates in patients with RCC, available literature indicates a clinical benefit.

Protocol for the application of bisphosphonates is variable. Dose and frequency of administration differ per study protocol in prospective studies and details are not always known in retrospective studies. In addition, several different types of bisphosphonates are used. When comparing these specific drugs, most is known about the effects of zoledronic acid, the most used bisphosphonate for BMs. In order to provide clear advice in the future, randomized control trials and prospective research with a clear administration protocol and specification of drugs applied are needed.

The timing to start patients on bisphosphonates as part of treatment of BMs is not clear. Guidelines are provided for other types of cancer. Osteonecrosis of the jaw is a known side effect for bisphosphonates (1%-12% of all patients, dependent on indication for either osteoporosis or cancer).[21] This typically occurs after 18 months of zoledronate use.[27] Smidt-Hansen et al[21] analyzed the rate of osteonecrosis of the jaw in patients with RCC receiving

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bisphosphonates and reported 23% osteonecrosis in patients treated with the combination of zoledronate and sunitinib, and only in 11% of patients with regular dental checks. They advise regular dental checkups before and during treatment for patients receiving bisphosphonates.

Although atypical femur fractures are extremely rare, their occurrence also increases with longer duration of bisphosphonate use.[28] However, it has not been reported that the incidence of atypical femur fractures increases when the bisphosphonates are given in higher dose and frequency in cancer patients compared to patients with osteoporosis, as is case for osteonecrosis of the jaw. Thus, there is no reason not to prescribe bisphosphonates for prevention of SREs in order to prevent atypical femur fractures in this patient group with low life expectancy.

In addition to the use of bisphosphonates in treatment for BMs, denosumab has been introduced to treat patients with RCC. This RANKL-inhibitor has recently shown superiority to zoledronate in preventing SREs in patients with advanced cancers (such as breast cancer and prostate cancer), without the additional adverse effects of renal toxicity and acute-phase reactions.[29] Bisphosphonates showed a risk reduction of 17% on the development of SREs and 14% on pathologic fractures in patients with advanced cancer of various types. The incidence of osteonecrosis of the jaw was similar for denosumab and zoledronate. Whether denosumab is a better option for prevention of SREs in patients with BM has not been studied in RCC.

Conclusion

In general, bisphosphonates seem to reduce the SRE rate in RCC patients with BMs. However, the level of evidence for the effect of bisphosphonates in patients with long BMs of RCC is still low.

Clinical Practice Points

- Our findings suggest that bisphosphonates alone reduce the SRE rate of BMs in RCC patients and showed a risk reduction of 55% on SREs in these patients when they are combined with radiotherapy. Bisphosphonates may be considered as a component of multimodal therapy strategy in patients with RCC and long BMs balancing the life expectancy and (rare) side effects.

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Disclosure

None.

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