Systematic Review

Skeletal-Related Events in Patients with Metastatic Renal Cell Carcinoma: A Systematic Review

Albert Jang[a], Shuang R. Chen[a], John Xie[a], Mehmet A. Bilen[b,c] and Pedro C. Barata[a,d]

[a]*Department of Medicine, Tulane University School of Medicine, New Orleans, LA, USA*
[b]*Department of Hematology and Medical Oncology, Emory University, Atlanta, GA, USA*
[c]*Winship Cancer Institute of Emory University, Atlanta, GA, USA*
[d]*Tulane Cancer Center, New Orleans, LA, USA*

Abstract. About one-third of advanced renal cell carcinoma (RCC) patients have bone metastases, which subsequently leads to the development of skeletal-related events (SREs), broadly defined to include surgery and radiation to bone, bone pain, pathological fracture, spinal cord compression, or hypercalcemia. The cumulative impact of SREs in RCC has not been well studied. SREs increase morbidity and mortality of RCC patients, although many interventions do significantly reduce their rates of development and improve prognosis. We performed a systematic review from the existing literature in PubMed from January 2002 through September 2019 and summarized the body of evidence regarding the development, prevention, prognosis and treatment of SREs in advanced RCC patients.

Keywords: Skeletal-related events, metastatic renal cell carcinoma, bone metastases, skeletal metastases, pathological fracture, bone-directed targeted therapies

INTRODUCTION

Renal cell carcinoma (RCC) is the sixth most common cancer diagnosed in men and the tenth most common cancer diagnosed in women worldwide [1]. The World Health Organization estimates there are over 175,000 deaths annually [2]. Distant metastases are present in almost one in five newly diagnosed cases [3]. The most common sites for RCC metastasis are lung, followed by bone and lymph nodes [4].

About one-third of advanced RCC patients have bone metastases (BM) [5], most commonly to the pelvis and lower lumbar spine [6]. The biology of bone metastasis is a complex process involving tumor, bone, and the immune system, which all produce cytokines, growth factors, and hormones promoting seeding in bone [7]. Notably, the interaction of RANK (receptor activator of NF-kB), RANKL (receptor activator of NF-kB ligand), and osteoprotegerin (OPG), which are regularly involved in bone remodeling, plays a major role [8]. These factors also make most RCC BM osteolytic lesions, which decreases bone integrity [9].

Decreased bone integrity contributes to skeletal-related events (SREs). The definition of SRE is variable in reported studies, yet most authors define it as: 1) surgery to BM, 2) bone pain requiring palliative radiotherapy or surgery, 3) pathological fractures, 4) spinal cord compression (SCC), and 5) hypercalcemia. SREs from different malignancies significantly decrease mobility and impair quality of

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Correspondence to: Pedro C. Barata, MD, MSc, Assistant Professor, Tulane University School of Medicine, Department of Internal Medicine, Section of Hematology and Medical Oncology, 1430 Tulane Avenue, New Orleans, LA 70112, USA. E-mail: pbarata@tulane.edu.

life in patients as well as increase the health-care burdens in society [10–14].

The overall impact of specific SREs in RCC patients has not been well-studied. In this systematic review from the existing literature from January 2002 through September 2019, we assess the development, prevention, prognosis and treatment of the different categories of SREs caused by RCC.

METHODS

Search strategy

A systematic literature search was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [15] to identify studies reporting on SREs of RCC between January 2002 and August 2019. The PubMed database was searched using one or combinations of the following keywords: "kidney cancer," "renal cell carcinoma," "bone metastases," "skeletal metastases," "skeletal related events," "pathological fracture," "impending fracture," "bone-directed targeted therapies," "cord compression," and "hypercalcemia." The selection process was conducted in two stages by the first and second authors independently: the first stage was performed via initial screening of the title and abstract to identify eligible publications. The second stage was done via full-text reading including a manual search of publications in journals not listed in PubMed to further avoid missing any eligible study.

For this systematic review, we excluded (I) non-English articles, (II) non-original articles (i.e. review articles with or without systematic review or meta-analysis), (III) editorials or case reports and (IV) repeated publications on the same cohort to avoid publication bias. The first and second authors individually performed initial screening of the title and abstract to identify eligible publications, then double-checked. Afterwards, full-text reading was performed by individual authors to narrow the number of manuscripts relevant to this review.

Data extraction

The following variables were extracted: subtype of renal cell carcinoma, palliative radiotherapy for bone pain, bone metastases and fractures requiring surgical intervention, spinal cord compression, hypercalcemia, and prevention of SREs with bone-modifying agents and molecular inhibitors.

Outcome measures

The rate of development of SREs in RCC and the outcomes of the SREs were the primary objective. A total of 187 manuscripts originally met criteria based on title, abstract, and references from other review articles. After screening, 54 manuscripts were included for this review (Fig. 1). The outcome data are reported by individual SRE; thus, each section may include data from the same publication.

RESULTS

Bone metastases and pathological fractures requiring surgical intervention

The rate of surgical intervention for those with BM in RCC (24%) was significantly higher than in prostate and urothelial cancers from a retrospective study of 650 patients with genitourinary cancers at eleven affiliated hospitals over a ten-year period in Japan, according to Owari et al. [16]. Despite the reported increase in surgical intervention, another study found that at one tertiary care center in the United Kingdom, surgery to bone and fracture as the first SRE was associated with better prognosis [5]. Kitamura et al. [17] found those who received surgery had a significantly prolonged median overall survival (OS) of 54.3 months versus 10.4 months without surgery ($p = 0.0002$). Du et al. [18] further noted those who underwent BM resection (33 patients) had longer OS than resection of any other site such as other organs (22 patients), with a median OS of 39.1 months versus 8.3 months, respectively.

The prolonged OS associated with surgery for BM may have been impacted by numerous factors, including RCC histology (clear cell versus non-clear cell type), the number and location of BM, the type of surgery itself, and comorbid conditions. Higuchi et al. [19] found that surgery for non-clear cell patients carried a worse prognosis with a median OS of 28 months versus 127 months for clear cell ($p = 0.01$), albeit with a limited sample size of 5 non-clear cell and 49 clear cell patients. Similarly, Lin et al. [20] found that one year after surgery, the OS rate was 51% for clear cell (248 patients) versus 25% for non-clear cell (47 patients).

The nature of the BM themselves also carry prognostic value. Fottner et al. [21] found that among 27 patients with solitary bone metastasis, 20 with multiple BM, and 54 with concomitant bone and visceral metastases, the solitary bone metastasis had signifi-

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│ Manuscripts identified through│
│   PubMed and references to review│
│ articles through title and abstract│
│       keywords (n=187)       │
└─────────────────────────────┘
               │              ┌─────────────────────────────┐
               │─────────────▶│ Initial exclusion of 38 manuscripts│
               │              │   based on abstract content  │
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│ Manuscripts with relevance to our│  │ Exclusion of 95 manuscripts │
│ study, assessed through full text, if│  │ • Unable to conclude data   │
│       available (n=149)      │  │   specifically for RCC due to│
└─────────────────────────────┘  │   inclusion of other        │
               │                  │   malignancies in the results│
               │─────────────────▶│   (n=55)                    │
               │                  │ • Duplicate studies (n=4)   │
               │                  │ • Could not find manuscript │
               │                  │   (n=6)                     │
               ▼                  │ • Number of cases <5 (n=8)  │
┌─────────────────────────────┐  │ • Hypercalcemia for reasons │
│ Manuscripts included in this review│  │   other than bone           │
│          (n=54)              │  │   metastases (n=11)         │
└─────────────────────────────┘  │ • No easily interpreted     │
                                  │   conclusions (n=4)         │
                                  │ • Other reasons (n=7)       │
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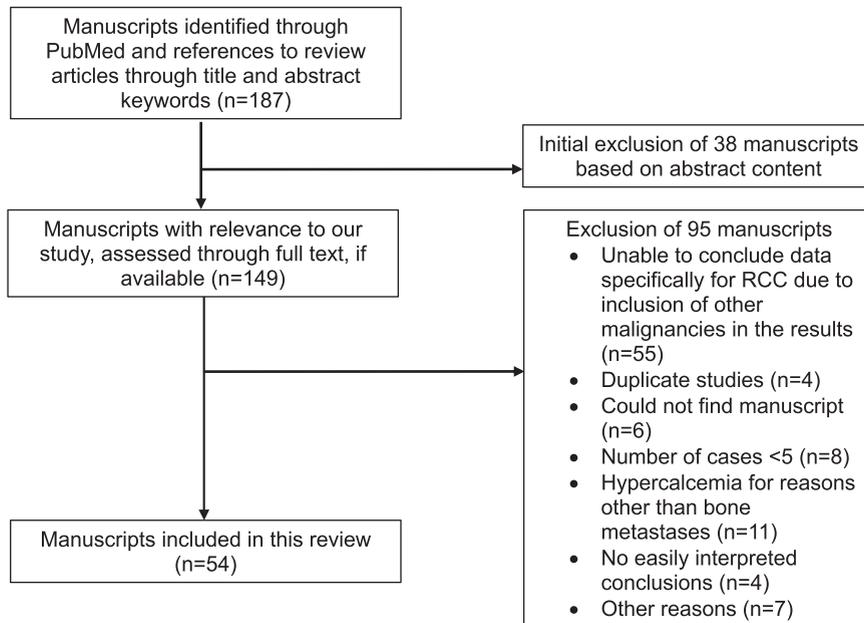
Fig. 1.

cantly better survival outcomes after BM surgery (60 months versus 30 months for multiple BM versus 12 months for visceral metastases, $p < 0.001$). Higuchi et al. [19] similarly concluded that metastasis to more than two sites were independent risk factors for a poor prognosis with a hazard ratio of 3.34 (CI 1.39 to 8.05, $p = 0.007$). The improved prognostic outcomes with resection of solitary BM have been corroborated through other studies [20, 22–26].

One controversial prognostic factor is the location of the BM. Higuchi et al. [19] further noted that the median OS after surgery was shortest for lesions in the pelvis compared to lesions in the spine or appendicular skeleton. Another study found that BM in the pelvic region were significant factors for both increased blood loss and poor performance status after surgery [27]. Yet, a third study found that axial location of metastases was associated with decreased OS [24]. However, two studies did not find a survival difference after surgical treatment based on the location of the BM [21, 25].

The type of operation also has debatable prognostic value. En bloc resection was described as a safe and effective treatment, with a five-year OS rate of 83% [28]. One retrospective study which included 183 patients (88 underwent metastasectomy, 54 had intralesional curettage, and 41 had stabilization only) found that the local recurrence rate was highest after stabilization only (39%), followed by

intralesional curettage (22%) and metastasectomy (12%) ($p = 0.003$) [29]. Survival was better in patients who underwent metastasectomy ($p = 0.020$), which increased further with negative margins ($p < 0.001$); however, after considering only patients with solitary metastasis (44/183), there was no survival difference ($p = 0.997$). One study found no difference in OS between en bloc resection and curettage [30]. Another study also found no difference in survival between the three procedure types [23].

Blood loss is a troubling complication of surgery for BM in RCC, given the highly vascular nature of the procedure. Preoperative embolization has been traditionally used to reduce bleeding risk, but more recent studies cast doubt on its utility. Jernigan et al. [31] found that among 1285 patients with femur metastasis who underwent stabilization, there was no difference in blood transfusion percentage between preoperative embolization (41/135 = 30%) and the control group (359/1150 = 31%). Two other studies found tumor size, rather than embolization itself, was a more important indicator of intraoperative blood loss [32, 33].

Bone pain requiring intervention

Diverse strategies have been attempted to relieve bone pain, including radiotherapy (RT) (most frequently), radiofrequency ablation (RFA), stereotactic

radiotherapy (SBRT), embolization, cementoplasty, and interleukin therapy, either as solo use or in different combinations.

Irradiating RCC BM could provide adequate pain relief, with average dosage generally ranging from 20–50 Gray (Gy). In Reichel et al. [34], 28 patients underwent irradiation to 36 sites (median total dosage 30 Gy) throughout the body (mostly along the spine); 25 sites did not need repeat RT, but the palliation was short term, as median time for pain to return to pre-RT levels was only two months. In Wilson et al. [35], 78 RCC patients received 143 palliative RT treatments (median dosage 20 Gy), in which 72 treatments were for bone pain at unspecified locations; overall, the authors concluded the palliative response using RT to bone was better than to other sites, such as the brain and lung. Similarly, from a phase 2 trial of palliative RT, 24 patients received RT for bone pain (unspecified locations), and 30 Gy in 10 fractions resulted in a significant response rate and pain relief measured by the modified McGill-Melzack scale [36]. Radiation (total dosage between 45–50 Gy) combined with immunochemotherapy (IL-2, IFN-alpha, and 5-fluorouracil) in 16 patients also provided remarkable pain relief [37]. However, another study of 19 RCC patients (9 were clear cell subtype) received IL-2 treatment to help relieve pain at various BM, with some patients receiving RT and/or surgery as well, and most patients continued to require analgesics afterwards [38].

Other successful methods of relieving bone pain in metastatic RCC include SBRT, embolization, cementoplasty and RFA. Jhaveri et al. [39] determined in 18 patients with clear cell RCC (total of 24 lesions to the spine, ribs, clavicles and pelvis), the most effective dose of SBRT for pain resolution was 40 Gy in 5 fractions, and there was a relationship between increased radiation dose and shorter time to stable pain relief. From a study of 107 patients receiving 163 embolizations using N-2-butyl cyanoacrylate to various sites (pelvis and vertebral column combined for over half), 157 had a clinical response with pain relief occurring within seven days [40]. Thirty transcatheter embolization procedures were used for 21 patients to treat 39 metastatic bone lesions (various locations, nearly half were pelvis), and 36 of the 39 sites achieved a clinical response lasting on average 5.5 months [41]. Five patients received cementoplasty for painful extraspinal BM (to the femur, acetabulum, and humerus), and for all cases, the visual acuity score (VAS) decreased immediately after treatment through an average of six months on follow-up

[42]. Combinations of these techniques have been employed as well. Both cementoplasty and percutaneous RFA applied to 6 RCC patients with 9 painful BM (humerus, pelvis, and spine locations) had a success rate of 100% with pain relief [43]. Pellerin et al. [44] analyzed 52 patients with 58 pelvic lesions using embolization, RFA, and cementoplasty; all procedures were successful, with a significant decrease in the VAS score at discharge along with one-month and six-month follow-up compared to the pre-procedure baseline VAS score.

Finally, cryoablation can also be used in such cases; however, the data in RCC is very limited and did not meet the inclusion criteria of this analysis [45, 46].

Spinal cord compression (SCC)

Over a ten-year period, out of 254 RCC patients in Europe (212 clear cell, 19 sarcomatoid, 7 poorly/undifferentiated, 4 chromophobe, 3 papillary, 2 unclassified, 2 other, 5 diagnosed radiologically), 68 (27%) developed SCC. Three other studies were from Asia. Over a five-year period, out of 94 RCC patients with BM in Yokomizo et al. [47], 13 patients (14%) developed SCC. Owari et al. [48] tracked 43 RCC patients with BM, and 10% of them developed SCC. Huang et al. [49] specifically documented 106 clear cell RCC patients with BM, and 46 (43%) developed SCC.

Three studies tried to identify potential prognostic factors associated with SCC [50–52]. In the study by Rades et al. [51] that included 71 elderly RCC patients with SCC who had received RT for relief; the authors developed a tool to best predict six-month survival rates, incorporating data of the time interval from RCC diagnosis to SCC diagnosis, number of visceral metastases at the time of RT, gait function at the time of RT, the time to developing motor deficits before RT, and ECOG performance. Similarly, in 30 clear cell RCC patients with SCC who received surgery, a prognostic (Tokuhashi) score included the patient's general condition, the number of spinal and extraspinal bone metastases, presence of visceral metastases, primary site of the cancer, and the severity of spinal cord palsy, with the most favorable having a score greater than 10 [52, 53].

Many different therapeutic methods have been used in SCC. Notably, 21 patients who received decompressive surgery for SCC in kidney cancer had increased survival after the operation relative to other cancers, including lung, breast, and

prostate [54]. In 25 patients with SCC who received preoperative embolization, it was noted greater embolization trended towards more blood loss, which suggested more extensive cord compression [55]. Six non-ambulatory patients, who received transcatheter arterial embolization then decompressive surgery plus stabilization of the vertebrae involved, had safely and significantly improved ambulatory function [56]. Another study by Rades et al. [57] compared 25 patients receiving short-course RT versus 87 receiving long-course RT; because both had a similar functional outcome, the short course of 1×8 Gy was the most recommended. Wilson et al. [35] analyzed 143 palliative RT treatment sites, 10 of which were for SCC, with variable success ranging from complete response to no response.

Hypercalcemia

Four manuscripts collected information on the number of cases of hypercalcemia secondary to BM in RCC. Woodward et al. [5] noted 31 patients (12%) of 254 RCC patients with BM (212 were clear cell) to have hypercalcemia. Yokomizo et al. [47] reviewed records of 511 genitourinary cancers with BM, including 94 RCC patients (56 of which were clear cell), and 10 of the 94 patients (11%) developed hypercalcemia, compared to metastatic prostate cancer (8/351 = 2%), bladder cancer (2/41 = 5%), and urothelial cancer (3/25 = 12%). Owari et al. [48] reviewed records of 180 genitourinary cancers with BM (43 RCC, 111 prostate cancer, 26 urothelial cancer). Up to 87 of the 180 received either zoledronic acid or denosumab, but it was unclear how many RCC patients received this intervention. As a whole, the frequency of hypercalcemia in the RCC subgroup was 10% (compared to 3% for prostate cancer, and 20% for urothelial cancer). Guillot et al. [58] reported 41 RCC patients (40 of which were clear cell carcinoma) treated with denosumab and an anti-angiogenic therapy; five cases (12%) developed hypercalcemia (one of whom also developed osteonecrosis of the jaw).

Prevention of SREs

Multiple studies have concluded potential benefits of bisphosphonates to reduce incidence of SREs and to prolong OS in bone metastatic RCC. Woodward et al. [5] conducted a comprehensive study that found a decrease of approximately 24% in the number of SREs in 53 patients with metastatic RCC who received multiple doses of bisphosphonate (pamidronate, zoledronic acid, clodronate, or alendronate) compared to 28 patients who received a single dose. Similarly, Lipton et al. [59] conducted a study with 74 RCC patients and compared outcomes of zoledronic acid versus placebo in addition to antineoplastic treatment and found that zoledronic acid significantly reduced the number of SREs. The mean skeletal morbidity rate (events per year), time to first SRE event, and median time to progression also improved. According to Santini et al. [60], RCC patients who received zoledronic acid had a median survival time of 15 months after BM diagnosis compared to seven months for patients without this agent, and there was a significant delay in time to first SRE from diagnosis in patients who received bisphosphonate compared to those who did not receive treatment. Yasuda et al. [61] found a longer OS in 23 patients who had received zoledronic acid compared to 22 patients who did not (80.8% versus 59.1% survival at one year, $p = 0.0034$).

Zoledronic acid has additionally been studied along with other treatment agents to evaluate its efficacy. Zoledronic acid was found to improve outcomes of patients who received this treatment in addition to RT compared to RT alone (although not always statistically significant) [62–64]. Hosaka et al. [64] demonstrated that treatment with sunitinib with the bisphosphonate improved the post-irradiation SRE-free rate. Zoledronic acid was also shown to work synergistically with everolimus, increasing median progression-free survival and median time to first SRE [65]. Other regimen combinations included zoledronate with statins, which did not demonstrate any significant changes in SREs in an eleven-patient group [66], and zoledronate, thalidomide, and interferon-gamma, which together was well-tolerated and potentially clinically beneficial [67].

However, other studies achieved different conclusions regarding efficacy of bisphosphonates. In a study by McKay et al. [68], in 2,749 patients who were treated with different angiogenic therapies (sunitinib, sorafenib, axitinib), temsirolimus or interferon-alpha, 28% had bone metastasis. The use of bisphosphonates was not associated with improved OS (13.3 versus 13.1 months, respectively; $p = 0.3801$), improved progression free survival (5.1 versus 4.9 months, respectively; $p = 0.1785$), or decreased rate of SREs (8.6% versus 5.8%, respectively; $p = 0.191$). Bisphosphonate use was also noted to be associated with increased hypocalcemia, renal insufficiency, and osteonecrosis of the jaw ($p < 0.0001$). The combination of a bisphosphonate

and targeted therapy (sunitinib, sorafenib, bevacizumab, temsirolimus, everolimus, pazopanib, or IL-2–based immunotherapy) did provide clinical efficacy [69, 70], although it was observed to cause higher rates of osteonecrosis of the jaw and therefore warrants consideration of oral and maxillofacial exams before and during treatment [70].

Besides bisphosphonates, other agents have been studied that decrease the rate of SREs, such as denosumab. Denosumab, which has been used to reduce SREs in other malignancies including breast cancer, might have a more pronounced toxic profile when combined with anti-angiogenic therapy, as noted in Guillot et al. where 7 of 41 RCC patients receiving denosumab and a tyrosine kinase inhibitor together developed osteonecrosis of the jaw [58].

Finally, in a post hoc analysis of the METEOR trial, where 253 RCC patients receiving cabozantinib were compared to 263 patients treated with everolimus, those who received cabozantinib presented with a lower rate of SREs (23% compared to 29%) [71].

DISCUSSION

Overall, the diversity and number of studies included in our literature review limits the ability to definitively conclude the rate of development of SREs in patients with metastatic RCC to the bone, but it is evident that SREs play a major role in morbidity and quality of life for these patients. There may be an increased rate in the development of SREs in RCC relative to other genitourinary cancers [16, 47], suggesting an increased awareness for these events is needed for these patients and their health care providers. Many different interventions for SREs including surgery, radiation, cementoplasty, embolization, bone modifying-agents, and molecular inhibitors have been investigated.

For patients with BM and pathological fractures, surgical intervention may provide a better prognosis and longer median OS under favorable conditions. Factors that improved surgical outcomes include clear-cell histology and solitary bone metastasis. Conversely, non-clear cell histology and metastasis to multiple sites were poor risk factors. The location of the BM and type of surgery has debatable prognostic value based on current literature.

Clear cell RCC appears to have a better prognosis than non-clear cell RCC from the standpoint of outcomes from SREs. The data is sparse, as few studies included in this review broke down the subtypes of RCC, and even fewer commented on the differences in outcomes between clear cell versus non-clear cell RCC. More research needs to be done in this area tailored towards distinguishing the many subtypes of RCC in terms of the rate of BM, prognosis and treatment outcomes.

Successful strategies implemented to counteract bone pain in RCC include irradiation of BM by SBRT, RFA, embolization, and cementoplasty. Radiation implemented together with other strategies including interleukins and surgery also have demonstrated successful pain management. However, most of these studies had small sample sizes, and studies with larger cohorts should be performed to better assess these methods.

Similarly, the use of RT, bisphosphonates, small-molecule inhibitors, surgery, and embolization have all been attempted to prevent the number of cases of malignant SCC or to emergently relieve them when they occur, with mixed results. It is possible these may be applied to decrease their morbidity and mortality, but more studies need to be done on preventing SCC in RCC patients.

Hypercalcemia is a known negative prognostic risk factor by the Memorial Sloan-Kettering Cancer Center (MSKCC) and the International Metastatic RCC Database Consortium (IMDC) [72, 73]. Bone-modifying agents such as bisphosphonates have been used in the treatment of malignant hypercalcemia and BM in several carcinomas including lung, breast, and prostate cancers, but they may be underused in patients with RCC [74]. In addition, in other solid tumors such as breast cancer, there is data suggesting an association between the expression of RANK on circulating tumor cells and denosumab effectiveness [75]. Despite the absence of definitive efficacy data and potentially significant side effects – such as osteonecrosis of the jaw – their use in RCC is associated with a reduction in the incidence of SREs and may be associated with a survival benefit.

Research continues for the molecular mechanisms of metastatic tumors reaching bone, which may lead to better treatments against the formation of BM in the first place. Metastatic bone lesions occur through a complex process in which cancer cells occupy bone erythropoietic system and induces immune cells to release factors that attract and stimulate osteoclasts [74]. Bisphosphonates oppose this process to some extent by reducing osteoclast development from precursors, disrupting bone resorption, inhibiting angiogenesis, and reducing interleukin-6 production from bone stromal cells [66]. The receptor c-MET has

been noted to be overexpressed in clear cell RCC [76], and c-MET signaling appears to play a role in bone metastasis [77]. The use of a c-MET inhibitor on RCC stem cells injected into bone inhibited the development of bone metastasis [78]. Cabozantinib is a small molecule kinase inhibitor against MET, VEGFR2, and other receptor tyrosine kinases [79]. As mentioned previously, cabozantinib decreased the number of SREs compared to everolimus in the METEOR trial, likely through affecting osteoblast and osteoclast activity through RANK, RANKL, and OPG [80]. Because RCC has been found to have RANKL and RANK mRNA correlate positively with primary tumor stage, and elevated RANKL and RANK expression was found to be a significant predictor for bone metastasis, additional insight into their interactions may shed further light into new inhibitors [81].

In addition, further research will continue to explore new treatment combinations of available drugs and strategies along with novel therapies to combat the development and minimizing the poor prognoses of SREs in RCC. Several clinical studies specifically investigating these questions are currently underway. A phase 2 study (RadiCaL study, NCT04071223) is testing the addition of radium-223 dichloride (an α-emitting radionuclide that successfully delays time to SREs in metastatic prostate cancer [82, 83]) to cabozantinib in metastatic advanced RCC to the bone. A different phase 2 study (KEYPAD, NCT03280667) is combining pembrolizumab and denosumab in clear cell RCC patients. A larger phase 3 study (MOSCAR, NCT03408652) will assess the efficacy and safety of denosumab and zoledronic acid for BM in RCC patients treated with targeted therapies. Other studies include bone pain as an endpoint in their clinical designs (e.g., NCT00920816).

The strengths of this literature review include an exhaustive search to examine the different broad categories of SREs specifically focused on RCC in peer-reviewed published literature over the last two decades. We also reviewed therapies and medications that increase the time to development of SREs and prevent their incidence and summarize the areas that need further research in order to gain a better understanding of these SREs.

By contrast, the limitations of this study include the heterogeneity of the patient population, the lack of prospective randomized studies, and the paucity of data specifically in RCC. Manuscripts that studied the rate of development of SREs or the rate for needing intervention (specifically for SCC and hypercalcemia) were included, but if specific studies analyzed fewer than five cases of the SRE of interest (especially surgical or bone pain relief cases), these were excluded due to the low significance. Finally, the financial burden of SREs in patients with RCC was not addressed, including the length of stay of hospital admissions and costs of procedures and medications.

In summary, SREs negatively impact RCC patients with BM. Diverse therapies exist for their prevention and treatment, but improved clinical outcomes must be weighed against adverse effects. More studies are needed as several gaps of knowledge exist, including the prognoses of different subtypes of RCC leading to SREs and the continued search for better prevention and treatment strategies. Current clinical trials are underway to study novel ideas and different combinations to minimize occurrences of SREs and improve prognosis.

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AUTHOR CONTRIBUTIONS

AJ, SRC: performance, interpretation of data; JX, MAB: interpretation of data; PCB: conception, interpretation of data.

CONFLICT OF INTEREST

MAB has acted as a paid consultant for and/or as a member of the advisory boards of Exelixis, Bayer, BMS, Eisai, Pfizer, AstraZeneca, Janssen, Genomic Health, Nektar, and Sanofi and has received grants to his institution from Xencor, Bayer, Bristol-Myers Squibb, Genentech/Roche, Seattle Genetics, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Peleton Therapeutics, and Pfizer for work performed as outside of the current study.

PCB has served in a consulting or advisory role for Bayer, Bristol-Myers Squibb, Pfizer, EMD Sorono, Eisai, Caris Life Sciences, Clovis, and Dendreon. PB has also received research funding from Blue Earth Diagnostics.

The other authors have no conflicts of interest to declare.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/KCA-200087.

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