**Supplementary Table**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Bone metastases and fractures requiring surgical intervention** | | | | | | |  |
| Author | Year | Number of RCC pts needing surgery/ Total number of RCC pts | Type of surgery | Indication | Sites | Question studied | Relevant surgical outcomes |
| Owari (16) | 2019 | 14/58 | N/A | N/A | N/A | hormone‐sensitive prostate cancer (HSPC) (n = 443) vs castration‐resistant prostate cancer (CRPC) (n = 50) vs renal cell carcinoma (n = 80) vs urothelial carcinoma (UC) (n = 77) | Of 58 patients with RCC who had developed SREs (defined in this manuscript as pathological fracture, SCC or the need for palliative RT/surgical intervention), 14 patients (24%) received surgical interventions for BM, which was significantly more than in patients with other cancers (9/88 for HSPC, 0/17 for CRPC, and 1/34 for UC). |
| Higuchi (19) | 2018 | 58/58 | en bloc metastasectomy in 46 patients (including 33 patients of total en bloc spondylectomy) and intralesional curettage in 12 patients | bone or soft tissue metastases | spine (n=33), appendicular skeleton (n=10), pelvis (n=8), thorax (n=4), soft tissue (n=3) | type of surgery and location on overall survival (OS), other risk factors for a poor prognosis | Median survival time (MST) was 127 months for en bloc metastasectomy and 54 months for intralesional curettage and bone grafting. MST was 127 months for the spine, 140 months for lesions of the appendicular skeleton, and 54 months for the pelvis. Non-clear cell type RCC and metastases to more than two sites were independent risk factors for a poor prognosis. |
| Jernigan (31) | 2018 | 1285/1285 | prophylactic fixation (all) | impending pathologic femur fractures | femur (all) | 135 patients who underwent preoperative embolization vs 1150 patients who did not undergo preoperative embolization | No difference in transfusion percentage was observed between preoperative transarterial embolization (41 of 135 [30%]) and the control group (359 of 1150 [31%]; relative risk, 0.973; 95% confidence interval, 0.743-1.274; p = 0.84). Preoperative embolization may not be mandatory in the prophylactic treatment of metastatic RCC of the femur. |
| Yoshiyama (27) | 2017 | 61/61 | fixation or intralesional curettage (n=14), wide resection of the metastasis (n=47) | BM | femur (n=29), humerus (n=15), tibia (n=4), pelvis (n=4), rib (n=3), radius (n=2), sternum (n=2), unknown (n=2) | intraoperative blood loss, postoperative performance status (PS), time to lethal events, postoperative complications | Location of a metastatic lesion in the lower extremities, multiple BM, multiple systemic metastases, impending/pathological fracture, palliative surgery, an unresectable primary lesion, and a poor preoperative PS were significant risk factors for a poor postoperative PS in univariate analysis. |
| Kitamura (17) | 2016 | 20/149 | resection (n=11), curettage (n=7), spinal fusion (n=2) | N/A | humerus (n=8), rib (n=3), vertebra (n=3), femur (n=5), tibia (n=1) | impact of surgery for BM on OS | Surgery for BM (HR=0.42, 95% CI=0.20-0.81, p=0.0085) was an independent prognostic factor and should be recommended for RCC patients. |
| Du (18) | 2016 | 33/114 | bone metastasectomy | metastasis to the spine and imminent fracture endangering the spinal cord (n = 13), unstable femur fracture (n = 5), or solitary bone metastasis (n = 17) | axial bones (spines, skulls, and ribs) (n=47), the appendicular skeleton (extremities, pelvis, clavicle, and scapula) (n=20), patients with a combination of both (n=33), exact locations could not be retrieved from the database (n=14) | bone resection on OS | Median OS of patients with BM resection (n = 33), which was 39.1 months (95% CI: 13.9–64.2), was significantly longer than those of patients with resection of any other site (n = 22) and patients without metastasis (n = 59), which were 8.3 months (95% CI: 6.6–10.0) and 7.6 months (95% CI: 6.2–8.9), respectively. |
| Fukushima (30) | 2016 | 26/71 | en bloc resection (n=16), curettage (n=10) | BM | N/A | en bloc resection vs curettage vs radiotherapy (RT) vs no intervention | OS was comparable among patients treated with en bloc resection, curettage, and RT with BED ≥85 Gy; patients treated with en bloc resection, curettage, and RT with BED ≥85 Gy showed significantly better OS than those treated with RT with BED <85 Gy or no local therapy (p = 0.006). |
| Langerhuizen (29) | 2016 | 183/183 | metastasectomy (n = 88, margins: 64 negative; 20 positive; 4 unclear), intralesional curettage (n = 54), stabilization only (n = 41) | BM | appendicular skeleton | metastasectomy, intralesional resection, vs stabilization only | The recurrence rate differed and was highest after stabilization only (39%), followed by intralesional curettage (22%), and metastasectomy (12%) (p = 0.003). Survival was better in patients who underwent metastasectomy (p = 0.020). |
| Ratasvuori (33) | 2016 | 144/144 | marginal resection (n=45) vs intralesional resection (n=103) | BM | humerus, femur, pelvis (all non-spine) | effect of preoperative embolization and resection margin on intraoperative blood loss, operation time, and survival | There were no statistically significant effects on intraoperative blood loss of preoperative embolization of skeletal non-spinal metastases. Pelvic localization and large tumor size increased intraoperative blood loss. |
| Kato (26) | 2016 | 36/36 | spinal metastasectomy | solitary spine metastases | spine | survival rates of patients who underwent metastasectomy of solitary spinal metastases from RCC | Spinal metastasectomy can potentially prolong survival. Only the presence of liver metastases was significantly associated with short‐term survival after spinal metastasectomy. |
| Petteys (22) | 2015 | 30/30 | decompressive laminectomy vs en bloc resection with negative surgical margins | pain (n=21), neuro deficits (n=9) | spine | Tokuhashi score for patients with RCC spine metastases and compare expected and observed survival | Patients with low systemic disease burden and solitary spinal metastases can have long survival and benefit from excisional surgery. |
| Woodward (5) | 2011 | 72/254 | N/A | BM | N/A | N/A | Patients who have surgery to bone and fracture as their first SRE have the best prognosis. |
| Fottner (21) | 2010 | 101/101 | radical resections (n=8), wide excisions (n=18), marginal excisions (n=64), intracapsular excisions (n=26) | 36% had fractures, 11% had neuro deficit | solitary bone metastasis (n=27), multiple BM (n=20), concomitant visceral metastases (n=54) | factors potentially affecting the survival of patients after surgical treatment | Patients with solitary bone metastasis had a better survival (p < 0.001) compared to patients with multiple metastases. Age younger than 65 years (p = 0.036), absence of pathologic fractures (p < 0.001) and tumor-free resection margins (p = 0.028) predicted higher survival. |
| Assouad (28) | 2010 | 6/6 | wide surgical resection of the rib | isolated rib metastases | ribs | surgical wide resection as a safe and effective treatment for rib metastases | Overall five- and ten-year survival rates were 83 and 66.7%, respectively, suggesting surgical wide resection is a safe and effective treatment. |
| Szendroi (25) | 2010 | 65/65 | radical resection of solitary metastasis, intralesional removal of solitary metastasis, locally radical resection in the case of multiplex metastases, transfocal fixation | BM and fractures | axially (in the shoulder girdle and pelvis, with the vertebrae and sacrum excluded) (n=10), in the limbs (n=55) | factors influencing the survival of the patients from the aspect of BM surgery | The survival significantly improved if the BM were solitary, low Fuhrman grade, late onset, and radical surgery was performed. When the solitary metastasis was radically removed, 75.0% of the patients survived the first, and 35.5% the fifth, postoperative year. |
| Řehák (32) | 2008 | 15/15 | radical (wide resection) | all with spine metastases, 4 with neurological deficit | cervical spine area (n=3), thoracic spine (n=8), lumbar (n=3) and sacral (n=1) | features influencing perioperative blood loss: size and extent of tumor, complexity of surgical approaches and radicality of embolization | Metastasis size, extent of tumor, technical complexity of surgery and the completeness of preoperative embolization had an important effect on the amount of perioperative blood loss. |
| Lin (20) | 2007 | 295/295 (368 operations total) | curettage with cementing and/or internal fixation (214 tumors), en bloc resection (117), closed nailing (27), amputation (4), and other measures (6) | 163 pathological fractures, 205 impending fractures | extremities and pelvis | factors that may affect survival after surgical treatment of metastases of RCC | Patients with a solitary bone metastasis had a significantly better survival rate than all other groups (p < 0.0001), with 78% and 35% survival rates at one and five years after the surgery, respectively. Patients with bone-only metastases had a better prognosis than patients with pulmonary metastases (p = 0.009). The clear-cell histological subtype (84% of the cases) was associated with more favorable patient survival than other variants (p < 0.0001). At one year, OS rate was 51% for the patients with the clear-cell subtype compared with 25% for those with a non-clear-cell subtype. At five years, the overall survival rates were 12% and 0%, respectively. |
| Fuchs (23) | 2005 | 33/60 | surgical treatment for the unifocal metastases included wide resection or amputation in 13 patients, curettage and stabilization in 20 pts | solitary bony metastases | wide resection: (axial n=5, appendicular n=8); curettage: (axial n=4, appendicular n=16) | importance of the type of surgical treatment | Patients who had a surgical procedure had better survival rates compared with patients who had no surgical treatment or simple biopsy of the local lesion (p = 0.007), with survival rates of 91%, 60%, and 36% versus 73%, 27%, and 8%, at 1, 3, and 5 years, respectively. No survival and outcome advantage for patients who had wide local excision of the solitary lesion compared with patients who had stabilization with intralesional curettage. |
| Jung (24) | 2003 | 46/99 | wide resection (n=9), intralesional resection and stabilization (n=37) | relief of pain, restoration of ambulatory status, and avoidance of extended periods of functional disability | spine (65 lesions), femur (37 lesions), humerus (24 lesions), pelvis (21 lesions) | curative vs palliative intent | Despite unpredictable results, palliative surgical treatment may be justified for patients for whom the expected survival rate is poor. The axial location of a metastasis was a significant univariate factor associated with decreased survival (p = 0.001). Patients who had wide resection of an osseous renal metastasis had a significantly greater survival rate than patients who had marginal resection or nonoperative treatment. |
| **Bone pain requiring intervention** | | | |  |  |  |  |
| Author | Year | Number of RCC pts with bone pain needing intervention | Total number of sites needing intervention | Type of intervention | Sites | Question studied | Relevant outcomes |
| Pellerin (44) | 2013 | 52 | 58 | radiation, embolization, and cementoplasty | sacrum (17 sites), acetabulum (26 sites), Ilio-pubian/ischio-pubian arch (15 sites) | impact of pain relief and quality of life using radiation, embolization, and cementoplasty using Visual Acuity Score (VAS) and Brief Pain Inventory questionnaire | Median VAS score decreased from 7±1.4 (ranges 5–10) at baseline to 3±1.5 (ranges 0–6) at discharge, 2±1.5 (ranges 0–5) at 1 month (p<0.0001), and 2±1.6 (ranges 0–5) at 6 months. All patients had improvements in quality of life. |
| Rossi (40) | 2013 | 107 | 163 | transcatheter embolization | sternum (4 sites), lumbar spine (32 sites), sacrum (9 sites), pelvis (67 sites), humerus (11 sites), radius (2 sites), ulna (1 site), femur (29 sites) | effect of selective embolization for palliative treatment based on clinical response (defined as ≥50% reduction in pain ≥50% or greater reduction in analgesics doses, and no response was defined as <50% decrease) | A clinical response occurred in 157 embolizations, with mean duration of 10 months (range 1-12 months). |
| Jhaveri (39) | 2012 | 18 | 24 | stereotactic body radiation therapy (SBRT) | spine (14), rib/clavicle (4) | utility of SBRT in treatment of painful BM in clear cell RCC | Seventy-eight percent of patients achieved relief. Patients treated with BED >85 Gy achieved faster and more durable pain relief compared to those treated with BED <85 Gy. A decrease in time to patient relief after a change in treatment regimen to 8 Gy x 5 fractions. |
| Basile (42) | 2008 | 5 | 5 | cementoplasty | humerus, acetabulum (2), femur (2) | effectiveness of cementoplasty | Successful pain relief as demonstrated by the VAS score for all 5 patients. |
| Forauer (41) | 2007 | 21 | 39 | transcatheter embolization | pelvis (18), lower extremity (8), upper extremity (3), rib/chest wall (5), vertebrae (5) | effectiveness of embolization for palliative treatment based on clinical response (defined as a 50% or greater decrease in narcotic use, and no response as less than a 50% decrease) | Clinical response occurred at 36 of the 39 sites, determined by recorded analgesic/narcotic use. |
| Reichel (34) | 2007 | 28 | 36 | RT | shoulder (1), humerus (1), ulna (1), rib (3), spine (15), sacrum (1), sacroiliac (5), ilium (1), hip (5), femur (1) | palliative effect of RT in terms of pain relief, fracture prevention, and functional activity using radiation to bone metastases | Median times to return to pretreatment pain and functional levels were 2 months and 1 month, respectively. RT controlled pain in the short term. It may lower the risk of pathological fracture, which happened at just one site 3 weeks after irradiation. |
| Lee (36) | 2005 | 24 | N/A | RT | N/A | palliative effect of RT based on reported pain, analgesic use, symptoms, and quality of life using validated questionnaires before RT, 1 month and 3 months after treatment, and every 3 months to 1 year afterwards | Overall, 30 Gy given in 10 fractions provides significant response in pain relief and improvement in quality of life. |
| Toyota (43) | 2005 | 6 | 7 | percutaneous radiofrequency ablation with cementoplasty | humerus (2), ilium (2), femur, sacrum, maxilla | efficacy and safety of percutaneous radiofrequency ablation with cementoplasty | Initial pain relief was achieved in all RCC patients. |
| Brinkmann (37) | 2005 | 16 | N/A | RT with immunochemotherapy (IL-2, IFN-alpha, and 5-fluorouracil) | N/A | effectiveness of combined immunochemotherapy (ICT) and radiation therapy (RT), based on pain medications given before and after treatment | Combination of RT with immunochemotherapy is feasible in reducing pain. |
| Adiga (38) | 2004 | 19 | N/A | IL-2 | N/A | characterization of clinical features of BM in RCC patients treated with IL-2 | There was no significant effect on pain relief. Of the 19 patients, 16 had pain responses analyzed. Twelve required pain medications before, and nine still required them after receiving IL-2. One who did not require pain medications before required them after receiving IL-2. |
| Wilson (35) | 2003 | N/A | 72 | RT | N/A | experience with palliative RT in RCC patients | Most common indication for RT in RCC patients was for bone pain. Radiation for bone pain seemed to provide more durable pain relief relative to other metastatic sites. |
| **Spinal cord compression** | | |  |  |  |  |  |
| Author | Year | Number of RCC patients with SCC | Total number of RCC patients | Intervention |  | Question studied | Relevant outcomes |
| Owari (16) | 2019 | 7 | 80 | bone-modifying agents |  | prevention of SREs with bone-modifying agents in different genitourinary cancers from a multi-institutional study | For SCC development rates in different genitourinary cancers, it was 7/80 for RCC, 23/443 for hormone-sensitive prostate cancer, 1/50 for castration-resistant prostate cancer, and 4/77 for urothelial carcinoma. It was unclear which patients received bone-modifying agents. |
| Huang (49) | 2019 | 46 | 106 | N/A |  | prognosis and outcomes for clear cell RCC patients with BM | Overall, clear cell RCC outcomes are poor, with unfavorable risk stratification. |
| Guillot (58) | 2019 | 4 | 41 | denosumab and anti-angiogenic therapy |  | toxicity profile in patients with metastatic RCC treated with denosumab and anti-angiogenic therapy | Four of 41 patients developed SCC, none of whom developed osteonecrosis of the jaw. |
| Owari (48) | 2018 | N/A | 43 | bone-modifying agents |  | incidence and risk factors for developing SREs in different genitourinary cancers from a single-institution study | There was a total of 7 cases of SCC among 180 total patients including prostate, urothelial, and renal cell carcinomas with metastases to the bone. Frequency of SCC was 14% for prostate cancer, 10% for RCC, and 0% for urothelial carcinoma. It was unclear which patients received bone-modifying agents. |
| Escudier (71) | 2018 | 14 | 658 | cabozantinib vs everolimus |  | subset of the METEOR trial, analysis of the bone-related outcomes | Six of 330 patients on cabozantinib developed SCC while 8 of 328 on everolimus developed SCC. |
| Rades (51) | 2016 | 71 | 71 | RT |  | method to predict survival of elderly patients with SCC from RCC | Longer interval from RCC diagnosis to SCC (p=0.019), lack of visceral metastases (p<0.001), slower progression of motor deficits (p<0.001), ambulation (p<0.001) and better performance status (p=0.002) were positive predictors. |
| Ivanyi (69) | 2016 | 6 | 82 | sunitinib |  | impact of BM in RCC patients on sunitinib, comparing metachronous vs synchronous BM | Six of 57 patients with synchronous BM developed SCC, while none of 25 patients with metachronous BM developed SCC. |
| Han (53) | 2015 | 30 | 30 | surgery |  | insights into clear cell RCC patients with SCC receiving surgery | Tokuhashi score of 10 or more was a favorable prognostic factor in clear cell RCC patients with SCC. |
| Smidt-Hansen (70) | 2013 | 2 | 21 | zoledronic acid and targeted therapy |  | safety and efficacy of zoledronic acid and targeted therapy | There was meaningful clinical activity with zoledronic acid with targeted therapy, however the risk of osteonecrosis of the jaw may be increased. |
| Morgen (50) | 2013 | 74 | 74 | N/A |  | prognosis of patients with metastatic cancer causing SCC, monitoring one-year survival rates in patients diagnosed with SCC 2005-2010 | Patients with SCC from pulmonary and renal cancers had improved survival. |
| Quraishi (55) | 2013 | 25 | 25 | preoperative embolization and surgery |  | surgical management of SCC in RCC patients who underwent preoperative embolization | Blood loss and complications are still major concerns for operative treatment of SCC, but 22/25 still improved or maintained stability neurologically. |
| Yasuda (61) | 2013 | 6 | 45 | zoledronic acid |  | impact of bisphosphonates on overall survival of RCC with BM | Six of 23 patients on placebo versus 0 of 22 patients on zoledronic acid developed SCC (p=0.0479). |
| Takeda (62) | 2012 | 2 | 27 | zoledronic acid and RT |  | comparison of outcomes of metastatic RCC patients receiving zoledronic acid with RT vs RT only | One of 15 patients receiving zoledronic acid and RT and one of 12 patients receiving RT only developed SCC. |
| Suzuki (56) | 2011 | 6 | 6 | direct decompressive surgery with stabilization (DDSS) of the vertebrae involved |  | outcomes of DDSS | All 6 patients regained ambulatory function within 2 months, and able to ambulate with assistance for 4-29 months (median 10 months). |
| Woodward (5) | 2011 | 68 | 803 | N/A |  | skeletal complications of RCC | Of 803 patients with RCC diagnosed at one institution from 1998-2007, 254 developed BM, of which 68 patients developed spinal cord/nerve root compression. |
| Yokomizo (47) | 2010 | 13 | 94 | N/A |  | incidence of SREs in urological cancer patients in Japan | Thirteen of 94 renal cancer patients had hypercalcemia, compared to 32/351 for prostate cancer, 2/41 with bladder cancer, and 4/25 with renal pelvic and ureteral cancer. |
| Chaichana (54) | 2009 | 21 | 21 | decompressive surgery |  | outcomes of decompressive surgery for different types of metastatic tumors causing epidural SCC | Patients with breast cancer, kidney cancer, or melanoma with SCC had the best outcomes after decompressive surgery compared to breast, GI, and lung cancers. |
| Kijima (63) | 2009 | 2 | 23 | zoledronic acid with RT |  | comparison of outcomes of metastatic RCC patients receiving zoledronic acid with RT vs RT only | Zero of 10 patients with zoledronic acid and RT and 2 of 13 patients with RT only had SCC. |
| Rades (57) | 2006 | 87 | 87 | RT |  | short-course RT (1x8 Gy, 5x4 Gy) versus long-course RT (10x3 Gy, 15x2.5 Gy, 20x2 Gy) RT after SCC | Short-course and long-course RT had no significant differences (p=0.91) |
| Wilson (35) | 2003 | 10 sites |  | RT |  | experience with palliative RT in RCC patients | For the spinal cord, two sites had complete response (resolution of symptoms), one site had partial response (improvement in symptoms without complete resolution), and three sites had no response. |
| Lipton (59) | 2003 | 5 | 46 | zoledronic acid (4 mg dose) |  | efficacy and safety of zoledronic acid in metastatic RCC patients, subset of ZOMETA trial | Two of 27 patients receiving zoledronic acid versus 3 of 19 who received placebo developed SCC. |
| **Hypercalcemia** | |  |  |  |  |  |  |
| Author | Year | Number of RCC pts with hypercalcemia | Total number of RCC patients |  |  | Question studied | Relevant outcomes |
| Guillot (58) | 2019 | 5 | 41 |  |  | analysis of toxicity profile of metastatic RCC patients treated with the combination of denosumab and anti-angiogenic therapy | Forty-one RCC patients were treated with denosumab and an anti-angiogenic therapy, and 1 of 4 patients who developed osteonecrosis of the jaw and 4 of 21 patients who did not have osteonecrosis of the jaw developed hypercalcemia (5/41). |
| Owari (48) | 2018 | 4 | 43 |  |  | incidence of SREs and risk factors in genitourinary cancer patients with newly diagnosed BM | There was a rate of 3% for prostate cancer, 10% for RCC, and 20% for urothelial carcinoma for 180 total patients with a genitourinary cancer. |
| Woodward (5) | 2011 | 31 | 803 |  |  | skeletal complications of RCC | Of 803 patients with RCC diagnosed at one institution from 1998-2007, 254 developed BM, of which 31 patients developed hypercalcemia due to BM. |
| Yokomizo(47) | 2010 | 10 | 94 |  |  | incidence of SREs in urological cancer patients in Japan | Ten of 94 renal cancer patients had hypercalcemia, compared to 8/351 for prostate cancer, 2/41 with bladder cancer, and 3/25 with renal pelvic and ureteral cancer. |
| **Prevention of SREs** | | |  |  |  |  |  |
| Author | Year | Number of RCC patients |  | Type of intervention | Question studied | SRE definition in the manuscript | Relevant outcomes |
| Guillot (58) | 2019 | 41 |  | denosumab and anti-angiogenic therapy | analysis of toxicity profile | fracture, surgery, palliative radiation, SCC, hypercalcemia pain | Seven of 41 patients developed osteonecrosis of the jaw, suggesting the importance of recognizing this toxicity when trying to prevent SREs. |
| Hosaka (64) | 2018 | 62 |  | RT, zoledronate with RT, and systemic treatment (including sunitinib, sorafenib, IFN-α, IL-2, everolimus, temsirolimus) | effectiveness of zoledronate, RT, sunitinib | pathological fracture, spinal palsy with ambulatory disorder, aggravating pain needing re-RT or surgery, impending fracture or palsy with radiological decline | There was no significant difference in survival between RT and zoledronate with RT (p=0.11), but post-irradiation SRE rate was significantly better in the RT and zoledronate group (p=0.02). SRE-free rate was significantly better in the sunitinib after RT group compared to RT only group (p=0.03). |
| Escudier (71) | 2018 | 658 |  | cabozantinib vs everolimus | bone-related outcomes of metastatic RCC in the METEOR trial | pathologic fractures, SCC, surgery to bone, external-beam RT to bone | For patients with BM at baseline, 23% of cabozantinib patients vs 29% of everolimus patients had SREs. For patients with no BM at baseline, 12% of cabozantinib patients vs 10% of everolimus patients had SREs. Time to first SRE was longer for cabozantinib compared to everolimus. |
| Ivanyi (69) | 2016 | 82 |  | sunitinib | impact of sunitinib on BM in metastatic RCC, comparing metachronous vs synchronous BM | bone radiation, SCC, pathological fracture, or bone irradiation | Patients with metachronous BM had improved survival compared to patients with synchronous BM, although sunitinib treatment efficacy for both types of patients was the same. Of the 82 patients, 48 developed SRE. |
| Broom (65) | 2015 | 30 |  | everolimus and zoledronic acid | effect of everolimus vs everolimus with zoledronic acid | pathologic fracture, surgical intervention to treat or prevent an impending fracture, RT to bone, SCC, hypercalcemia of malignancy | Median time to first SRE was 9.6 months with everolimus and zoledronic acid vs 5.2 months on everolimus only (p=0.009). Bone resorption markers were decreased with combination of everolimus and zoledronic acid relative to everolimus alone. |
| McKay (68) | 2014 | 2749 |  | sunitinib, sorafenib, axitinib, IFN-α, temsirolimus, temsirolimus plus IFN-α, bisphosphonates | effect of bisphosphonates | pain requiring radiation, pathologic fractures, SCC, surgery to bone, hypercalcemia | Bisphosphonates given to 285 patients did not have a decreased rate of SREs compared to non-users (8.6% versus 5.8%, p=0.191). Side effects of hypocalcemia, renal insufficiency and osteonecrosis of the jaw were increased in bisphosphonate users (p<0.001). |
| Santini (60) | 2013 | 398 |  | zoledronic acid | outcomes of bone disease in RCC | pathological fractures, RT for bone pain, surgical interventions to treat or prevent an impending fracture, spinal cord and nerve root compressions, hypercalcemia | At least 71% of patients developed an SRE. For 181 patients who received zoledronic acid, time to first SRE was 3 months compared to 1 month for patients who did not (p<0.05). |
| Smidt-Hansen (70) | 2013 | 21 |  | zoledronic acid with targeted therapy | safety and efficacy | pathological fracture, radiation to bone, surgery to bone, SCC | Combination of zoledronic acid and targeted therapy was beneficial for patients in terms of overall survival, although osteonecrosis of the jaw (which occurred only in patients getting zoledronic acid with sunitinib) may be increased. |
| Yasuda (61) | 2013 | 45 |  | zoledronic acid | impact of bisphosphonates on overall survival of RCC with BM | pathological fractures, SCC, use of palliative RT, need for orthopedic surgery | Zoledronate-treated group (23 patients) had a significantly lower SRE rate (0.87/year) compared to 22 patients who did not receive zoledronate (1.82/year, p=0.0453). |
| Takeda (62) | 2012 | 27 |  | zoledronic acid and RT | whether RT with zoledronic acid could prolong time to SRE compared to RT alone | pathologic fracture, spinal cord and cauda equina compression, RT to bone, surgery to bone, a change of anticancer therapy to treat bone pain, or hypercalcemia from malignancy | Three of 15 patients with zoledronic acid and RT compared to 6 of 12 patients with RT alone developed SRE, but there was no difference in overall survival time between the two groups. |
| Manoukian (66) | 2011 | 11 |  | zoledronic acid with fluvastatin or atorvastatin | whether bisphosphonates with statins could provide synergistic benefit | metastatic sites requiring RT or any surgical intervention (e.g., embolization, radiofrequency ablation, intrathecal catheter placement), or complications from skeletal metastatic lesions (e.g., pathologic fracture, SCC) | Of 11 patients who received zoledronate with fluvastatin or atorvastatin, 7 developed SREs (median time to development of 7 months). It was safe to combine both, although it did not appear to significantly increase time to SRE development. |
| Woodward (5) | 2011 | 803 |  | bisphosphonates | skeletal complications of RCC | hypercalcemia, spinal cord/nerve root compression, RT or surgery to bone, symptomatic fracture | Eighty-one patients received bisphosphonates (pamidronate [56.0%), zoledronic acid [46.4%], clodronate [4.8%], alendronate [1.2%]); 53 patients who received multiple doses of bisphosphonates had a decrease in 1.3 SREs |
| Kijima (63) | 2009 | 23 |  | zoledronic acid with RT | comparison of outcomes of metastatic RCC patients receiving zoledronic acid with RT vs RT only | pathological fracture, SCC, bone surgery, RT to the bone | One of 10 patients with RT and zoledronic acid compared to 10 of 13 patients with RT only developed an SRE (p=0.003). Median SRE survival time was not treated in the combined group but was 18.7 months in the RT only group (p=0.046). |
| Tannir (67) | 2006 | 15 |  | zoledronate, thalidomide, and interferon-gamma | efficacy and safety of zoledronate, thalidomide, and interferon-gamma | need for RT, surgical intervention, pathological fracture, SCC | Nine of 15 patients on this regimen developed SRE, with median time to development of 12.0 weeks. This regimen was well tolerated and may provide clinical benefit. |
| Lipton (59) | 2003 | 74 |  | zoledronic acid (4 mg and 8 mg doses) | efficacy and safety of zoledronic acid in metastatic RCC patients, subset of ZOMETA trial | pathologic fracture, SCC, RT, surgery to bone | Risk of developing an SRE while on zoledronic acid decreased the rate by 61% compared to placebo (HR=0.394, p=0.008) |