Editorial Commentary

Lack of evidence regarding bone metastases of genitourinary cancers: interventions by surgery, radiotherapy, and bone-targeted systemic therapy

Makito Miyake, Takuya Owari, Kiyohide Fujimoto

Department of Urology, Nara Medical University, Kashihara, Nara, Japan

Correspondence to: Makito Miyake, Department of Urology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan. Email: makitomiyake@yahoo.co.jp.

Provenance: This is an invited article commissioned by Section Editor Xiao Li (Department of Urology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China).

Comment on: Ruatta F, Derosa L, Escudier B, *et al*. Prognosis of renal cell carcinoma with bone metastases: Experience from a large cancer centre. Eur J Cancer 2019;107:79-85.

Submitted Apr 06, 2019. Accepted for publication Apr 12, 2019.

doi: 10.21037/atm.2019.04.52

View this article at: http://dx.doi.org/10.21037/atm.2019.04.52

Overview of a retrospective study from a high-volume cancer center

The bone is a major metastatic site of genitourinary (GU) cancer, especially in prostate cancer (PCa). Around 84–91% of patients with metastatic PCa harbor bone metastases (BMs), while the rates of BMs in patients with metastatic renal cell carcinoma (mRCC) and metastatic urothelial carcinoma of the bladder are reportedly 29% and 16–25%, respectively (1). Among mRCC cohorts, bone is the second most common metastatic site after the lungs (2,3).

Ruatta *et al.* recently reported on a large retrospective study that investigated the prognostication of RCC with BMs (4). Among 1,750 patients with RCC treated in Gustave Roussy Cancer Campus, 300 (17.1%) having BMs were included in the analysis. One of the distinctive points in this study was the clinical significance of synchronous solitary bone metastasis (SSBM), which was defined as a solitary BM without any other visceral metastases at the first diagnosis of RCC. The distribution of types of BMs included SSBM in 22 (7%) of 300 patients and multiple BMs and/or metachronous BMs in 42 (14%) patients. The remaining 236 (79%) patients had concomitant metastases in other sites. The unique characteristics of RCC BMs include the high frequency of solitary lesions (57%) and involvement of the long bone (31%). The median times to BM and overall survival (OS) were 32.4 and 23.2 months, respectively. In addition, 168 (56%) of the patients experienced at least one skeletal-related event (SRE). The median times to the first and second SRE were 5.3 and 10.8 months, respectively. Regarding the prognosis, SSBM patients showed significantly longer OS compared to that in non-SSBM patients. Multivariate analysis using a Cox regression model revealed that a better OS from the diagnosis of BMs was associated with the following four factors: good Memorial Sloan Kettering Cancer Center (MSKCC) risk group [P<0.05; hazard ratio (HR) =0.5; 95% confidence interval (CI) 0.38–0.67], SSBM (P=0.04; HR =0.66; 95% CI: 0.43–0.99), concomitant visceral metastases at the diagnosis of BMs (P<0.05; HR =2.02; 95% CI: 1.39–2.96), and surgery for BMs (P=0.01; HR =0.68; 95% CI: 0.50–0.93).

To the best of our knowledge, this is the largest single-center study to date to report the clinical history of BMs in patients with mRCC, demonstrating that MSKCC risk group, numbers of BMs, and radical resection of BM sites were significant predictors for survival after the diagnosis of BMs. The authors concluded that radical surgery for BMs should be considered for not only local tumor control but also for OS improvement in patients with solitary BM without concomitant metastases at the initial diagnosis of RCC.

Interventions for patients with BMs

Because BMs can cause substantial symptoms including

pain, pathologic fracture, spinal cord compression, and hypercalcemia, interventions using surgery, radiotherapy, and bone-targeted systemic therapy should be considered when patient performance and comorbidities allow. A systematic review by Dabestani *et al.* reported the benefits and harms of several types of local treatments for various metastatic organs in mRCC (5). Complete metastasectomy led to better survival and symptom control including significant relief from pain due to BMs as compared to those in patients treated with either incomplete or no metastasectomy. In this review, the authors selected three retrospective studies that exclusively focused on surgical or radiation interventions for BMs of mRCC (6-8).

The first publication, by Zelefsky *et al.*, compared tumor control outcomes between hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial BMs (6). A total of 105 BMs from RCC were irradiated with either single-dose radiotherapy (a prescription dose of 18–24 Gy) or hypofractionation (a prescription dose of 18–24 Gy per three or five fractions). The local progression-free survivals at three years after radiation for patients undergoing a high single-dose (24 Gy), a low single-dose (<24 Gy), and hypofractionation were 88%, 21%, and 17%, respectively. Multivariate analysis with adjustment for possible confounding factors identified high single-dose radiotherapy as an independent significant predictor for improved local tumor control. The second publication, by Hunter et al, compared the efficacy and durability on symptom control from painful spinal metastases between conventional external beam radiotherapy and single-fraction high-dose stereotactic body radiation (SBRT) (7). There was no statistical difference in pain relief in symptomatic spine BMs between conventional radiotherapy and SBRT. They concluded that the former should be used as first-line treatment. However, prospective study is warranted to explore the appropriate use of SBRT in this patient population. The third publication, by Fuchs *et al.*, evaluated the clinical significance of surgical intervention based on a retrospective analysis of 60 patients with solitary BMs from RCC (8). The survivals of patients undergoing metastasectomy (n=13) or local stabilization (n=20), or nonsurgical treatment (n=27) for BMs were compared. Although patients undergoing surgical interventions had longer OS compared to those without surgical interventions, no survival advantage was observed between metastasectomy and intralesional resection or intramedullary stabilization alone. The authors concluded that metastasectomy of a solitary BM from RCC is not mandatory to prolong OS but emphasized the need for any surgical intervention (complete or intralesional resection and stabilization) to prevent future SREs. Radical surgical intervention for spinal metastasis lesions in patients with mRCC can be selected to reduce the risk of developing spinal cord compression when patients are expected to have longer survival and with solitary spinal local metastasis. However, the negative aspects of radical surgery for spinal metastatic lesions include possible life-threating blood loss requiring a large amount of blood transfusion as spinal metastatic lesions from RCC are generally extremely hypervascular (9). Thus, radical surgery for spinal metastasis lesions should be considered cautiously for limited patients.

As most of the currently available evidence is based on retrospective analysis, high risks of bias were unavoidable across all studies. When the findings are interpreted with caution, they can provide guidance for urologists, clinicians, and researchers and directions for future investigation.

Other interventions for BM lesions

Gardner *et al.* reported a retrospective review of 40 patients (50 BM lesions) with mRCC who underwent cryoablation for BMs (10). The mean BM size was 3.4±1.5 cm and the median follow-up was 35 months. Cross-sectional imaging after cryoablation and follow-up data including procedure-related complications were reviewed to determine post-treatment local tumor control. The overall local tumor control rate was 82% (41 of 50 lesions). A better local tumor control rate was achieved in patients with oligometastatic disease compared to that in patients with >5 metastases (96% *vs.* 53.3%, P=0.001). The better local tumor control rate was associated with lesions with a larger difference between the maximum ice ball and lesion diameters. Three instances of grade-3 and one instance of grade-4 complications were observed (Common Terminology Criteria for Adverse Events, version 4).

There remains a lack of evidence for cryoablation in patients with BMs for RCC. However, the study by Gardner *et al.* demonstrated that this relatively less invasive modality may be an alternative treatment for local tumor control and quality of life, especially in patients with oligometastatic disease (10).

Predicting the prognosis of patients with BMs

Although target therapies such as tyrosine kinase inhibitors (TKIs) or mammalian target of rapamycin (mTOR)

inhibitors significantly improve survival in patients with mRCC (11), BMs are a predictor of shorter survival in the era of targeted therapy (12,13). In our previous study on the predictive risk factors for cancer-specific survival (CSS) in patients with metastatic GU cancers with BMs, the median CSS in mRCC with BMs was 29 months (1). Regarding the predictive factors of survival, Kitamura *et al.* from Japan reported the administration of molecular target therapy, MSKCC risk group, cytoreductive nephrectomy, and surgery for BMs to be prognostic factors in patients with BMs of RCC (14). This finding was similar to that reported by Ruatta *et al.* (4). Although MSKCC risk classification includes performance status and laboratory data containing serum levels of hemoglobin, calcium, and lactate dehydrogenase, these studies have not investigated each factor. We analyzed 180 patients with GU cancers, including 43 patients with BMs of RCC, to identify the risk factors that predicted CSS. In multivariate analysis, these included poor performance status, the presence of visceral metastasis, and laboratory data including neutrophil-lymphocyte ratio and Glasgow prognostic score calculated from C-reactive protein (CRP) concentration (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL). Surgical intervention was identified as a factor predicting survival by both Ruatta *et al.* (4) and Kitamura *et al.* (14). However, the limitations of the studies included their retrospective designs, determination for surgical interventions for primary and metastatic lesions at the discretion of individual physicians, and patient groups in both cytokine-therapy and TKI eras. Moreover, cytoreductive nephrectomy did not significantly improve progression-free survival compared to that of molecular targeted therapy alone in a recent RCT performed in the era of targeted therapy (15). Therefore, the roles of cytoreductive nephrectomy and surgical intervention for BM lesions in patients with BMs of RCC require further clinical investigation in the current era of targeted therapies and immune checkpoint inhibitors.

SREs due to BMs of urogenital cancers

Because BMs lesions in patients with mRCC are predominantly osteolytic, they cause decreased bone integrity and severe bone pain. These factors result in SREs including pathological fracture, spinal cord compression, which require surgery or radiotherapy to the BMs lesions. Moreover, recent clinical trials have proposed the use of symptomatic skeletal events (SSEs) as a new end-point that is more directly related to patient quality of life (16). SSEs are defined as events requiring radiotherapy and surgical intervention to relieve skeletal symptoms, new symptomatic pathological fractures, spinal cord compression. SREs and SSEs can result in reduced activity of daily life and increased healthcare burdens due to severe pain and increased analgesic medication and opioid use. Therefore, preventing SREs is vital for the management of patients with BMs. Our previous large retrospective study revealed that 72.5% of patients with BMs of RCC developed SRE at least once and that the median time to first SREs in these patients was 10 months after the diagnosis of BMs (17). An Italian multicenter-based survey (18) reported a similar finding, in which 71% of 398 patients with BMs of RCC developed SREs. Bone-modifying agents (BMAs) such as zoledronic acid (ZA) and denosumab have been clinically proven to prevent SREs in various cancers with BMs, including castration-resistant PCa in the field of GU cancers (19). Moreover, a recent review by von Moos *et al.* (20) suggested that BMAs could relieve pain, prolong the time to first analgesic medication and opioid use, and improve patient quality of life. Although the incidence of SREs is significantly higher in RCC than that in PCa (17,18), evidence supporting the efficacy of BMAs in patients with mRCC is still limited. A retrospective subset analysis of patients with mRCC enrolled in a multicenter, randomized, placebo-controlled study revealed that ZA significantly reduced the incidence of SREs (37% *vs.* 74% for placebo; P=0.015) and prolonged the median time to first SREs (not reached *vs.* 72 days for placebo; P=0.006). In addition, in a randomized controlled trial , Broom *et al.* demonstrated that everolimus combined with ZA prolonged the median time to first SRE compared to that for everolimus monotherapy (9.6 *vs.* 5.2 months; P=0.03) (21). With regard to denosumab, a human monoclonal antibody against receptor activator of nuclear factor-kappa B ligand (RANKL), no specific analysis on the efficacy of denosumab in patients with mRCC with BMs has been reported. In a randomized phase III trial including 155 (10%) patients with RCC among 1,597 patients with solid tumors excluding prostate and breast cancers, denosumab significantly prolonged the time to first SREs compared to ZA (HR =0.81, 95% CI: 0.68–0.91, P=0.017) (22). Moreover, in a subgroup analysis of patients with RCC, the estimated reduction rate for first SREs was 29% in the denosumab group compared to that in the ZA group. In our previous retrospective study on the clinical benefit of early treatment with BMAs, defined as the administration of BMAs within 6 months from the diagnosis of BM, the median time to first SRE in the early treatment

group (87 months) was significantly longer than that in non-user group (6 months) (P=0.003) in mRCC patients with BMs (17).

Based on recent findings, BMAs could be recommended for the management of patients with mRCC. Moreover, a few series of retrospective analyses demonstrated that combination therapy such as targeted therapy or radiotherapy plus BMAs could improve survival or SRE-free rates (23-25). In the current era of TKIs and immune checkpoint inhibitors, further evidence is needed to indicate the clinical benefit of such combination therapies and to establish the appropriate management of patients with mRCC with BMs. However, the selection of these combination therapies requires more close attention to adverse events, especially medication-related osteonecrosis of the jaw (MRONJ) following reports from Keizman *et al.* that TKIs combined with bisphosphonate were associated with an increased incidence of MRONJ (23).

Concluding remarks

There remains a significant lack of evidence regarding BMs of GU cancers, particularly in RCC and urothelial carcinoma. The presence of BMs is strongly associated with shorter survival. The strategy of clinical management for BMs such as timing and types of interventions by surgery, radiotherapy, and bone-targeted systemic therapy has not yet been fully established. Molecular target therapies and immune checkpoint inhibitors have dramatically improved survival of mRCC. Aggressive intensive treatments such as cytoreductive nephrectomy or surgical intervention to BM lesions could be selected if patients are expected to have a long prognosis based on risk stratification.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Owari T, Miyake M, Nakai Y, et al. A Genitourinary Cancer-specific Scoring System for the Prediction of Survival in Patients with Bone Metastasis: A Retrospective Analysis of Prostate Cancer, Renal Cell Carcinoma, and Urothelial Carcinoma. Anticancer Res 2018;38:3097-103.
2. Coleman RE. Monitoring of bone metastases. Eur J Cancer 1998;34:252-9.
3. Zekri J, Ahmed N, Coleman RE, et al. The skeletal metastatic complications of renal cell carcinoma. Int J Oncol 2001;19:379-82.
4. Ruatta F, Derosa L, Escudier B, et al. Prognosis of renal cell carcinoma with bone metastases: Experience from a large cancer centre. Eur J Cancer. Eur J Cancer 2019;107:79-85.
5. Dabestani S, Marconi L, Hofmann F, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. Lancet Oncol 2014;15:e549-61.
6. Zelefsky MJ, Greco C, Motzer R, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. Int J Radiat Oncol Biol Phys 2012;82:1744-8.
7. Hunter GK, Balagamwala EH, Koyfman SA, et al. The efficacy of external beam radiotherapy and stereotactic body radiotherapy for painful spinal metastases from renal cell carcinoma. Pract Radiat Oncol 2012;2:e95-100.
8. Fuchs B, Trousdale RT, Rock MG. Solitary bony metastasis from renal cell carcinoma: significance of surgical treatment. Clin Orthop Relat Res 2005;431:187-92.
9. Rehák S, Krajina A, Ungermann L, et al. The role of embolization in radical surgery of renal cell carcinoma spinal metastases. Acta Neurochir (Wien) 2008;150:1177-81; discussion 1181.
10. Gardner CS, Ensor JE, Ahrar K, et al. Cryoablation of Bone Metastases from Renal Cell Carcinoma for Local Tumor Control. J Bone Joint Surg Am 2017;99:1916-26.
11. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584-90.
12. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449-56.
13. Pal SK, Ghate SR, Li N, et al. Real-World Survival Outcomes and Prognostic Factors Among Patients Receiving First Targeted Therapy for Advanced Renal Cell Carcinoma: A SEER-Medicare Database Analysis. Clin Genitourin Cancer 2017;15:e573-82.
14. Kitamura H, Takahashi A, Takei F, et al. Molecular-targeted Therapy and Surgery May Prolong Survival of

Renal Cell Carcinoma Patients with Bone Metastasis: A Multi-institutional Retrospective Study in Japan. Anticancer Res 2016;36:5531-6.
15. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 2018;379:417-27.
16. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213-23.
17. Owari T, Miyake M, Nakai Y, et al. Clinical benefit of early treatment with bone-modifying agents for preventing skeletal-related events in patients with genitourinary cancer with bone metastasis: A multi-institutional retrospective study. Int J Urol 2019. doi:10.1111/iju.13939.
18. Santini D, Procopio G, Porta C, et al. Natural history of malignant bone disease in renal cancer: final results of an Italian bone metastasis survey. PLoS One 2013;8:e83026.
19. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377:813-22.
20. von Moos R, Costa L, Ripamonti CI, et al. Improving quality of life in patients with advanced cancer: Targeting metastatic bone pain. Eur J Cancer 2017;71:80-94.
21. Broom RJ, Hinder V, Sharples K, et al. Everolimus and zoledronic acid in patients with renal cell carcinoma with bone metastases: a randomized first-line phase II trial. Clin Genitourin Cancer 2015;13:50-8.
22. Henry D, Vadhan-Raj S, Hirsh V, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. Support Care Cancer 2014;22:679-87.
23. Keizman D, Ish-Shalom M, Pili R, et al. Bisphosphonates combined with sunitinib may improve the response rate, progression free survival and overall survival of patients with bone metastases from renal cell carcinoma. Eur J Cancer 2012;48:1031-7.
24. Beuselinck B, Wolter P, Karadimou A, et al. Concomitant oral tyrosine kinase inhibitors and bisphosphonates in advanced renal cell carcinoma with bone metastases. Br J Cancer 2012;107:1665-71.
25. Hosaka S, Katagiri H, Niwakawa M, et al. Radiotherapy combined with zoledronate can reduce skeletal-related events in renal cell carcinoma patients with bone metastasis. Int J Clin Oncol 2018;23:1127-33.

Cite this article as: Miyake M, Owari T, Fujimoto K. Lack of evidence regarding bone metastases of genitourinary cancers: interventions by surgery, radiotherapy, and bone-targeted systemic therapy. Ann Transl Med 2019;7(Suppl 3):S92. doi: 10.21037/atm.2019.04.52

