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Clear cell renal cell carcinoma bone metastasis: What should be considered in prognostic evaluation

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ABSTRACT

Introduction: Knowledge of clear cell renal cell carcinoma bone metastasis (ccRCC-BM) remains scarce. This study depicts clinical, pathological and outcome features of the disease and provides suggestions to establish prognosis prediction system more appropriate for ccRCC-BM.

Materials and methods: Patients with ccRCC-BM had clinical, pathological data collected. Kaplan-Meier survival analysis was used for outcome profiles. Prognostic risks were evaluated using MSKCC/Motzer score. Univariate and multivariate logistic regression were performed to investigate association between clinical, pathological features and prognosis.

Results: In the series containing 106 ccRCC-BM patients with 4:1 male predominance, 44.3% of them had synchronous bone metastasis and 28.3% had multi-organ metastasis. Axial bone was prone to bone metastasis and the incidence of severe skeletal-related events was 54.7%. Curative bone lesion resection was performed in 70.7% patients. The median overall survival (mOS) time was 45 months for all and 32 months for those in unfavorable risk stratification. Shorter time to bone metastasis (TTBM) [OR 1.019, 95% CI (1.007, 1.031)], elderly age [OR 1.040, 95% CI (1.001, 1.080)], concomitant multi-organ metastasis [OR 3.883, 95% CI (1.375, 10.967)] and carbonic anhydrase (CA)-IX expression loss [OR 58.824, 95% CI (2.653, 1000)] were associated with poor prognosis.

Conclusion: The outcome of ccRCC-BM remained poor in unfavorable risk stratification. Bone lesion resection accompanied by systematic therapy for selected patient could improve prognosis. Shorter TTBM, elderly age, concomitant multi-organ metastasis and the expression loss of CA-IX along with gender-bias, feasibility for surgical treatment are suggested to be incorporated in modified ccRCC-BM-specific prognosis prediction system.

Introduction

Metastatic renal cell carcinoma (mRCC) exhibits in a quite amount of patients, despite that more local RCC could be early detected and well managed with the advancement of imaging and surgical techniques. For those, mRCC might be found in their first diagnoses or after the curative procedures. Bone is the second-most metastasis site right after lung [1]. About 30%–50% patients with advanced RCC were found to have bone metastasis (RCC-BM) [2,3].

Clear cell RCC (ccRCC), representing the most common histology, has worse prognosis comparing to papillary RCC and chromophobe RCC [4–6]. Also, ccRCC patients have higher incidence of bone metastasis [1]. Several local and systematic therapies, including orthopedic surgeries, radiotherapies and medication therapies have been introduced in the management of ccRCC-BM [7–9] with the desire to extend the overall survival (OS) time. Though those epidemiological profiles, therapeutic strategies and even pathogenesis mechanism have well discussed before [10,11], knowledge on the aspect of bone lesion remains scarce and the following questions need to be noted.

As no therapeutic standard or guideline currently exists for RCC-BM, decisions for those patients were usually made empirically and based on the prognosis prediction. Since essential predictive systems for mRCC are not specifically designed for bone metastasis, in which clinical, pathological features of bone lesion were not

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included, the application for ccRCC-BM is largely limited.

In this study, we summarized the clinical, pathological and outcome profiles of ccRCC-BM using a large population-based series. Furthermore, we attempted to provide suggestions and complements to establish a prognosis prediction system appropriate for ccRCC-BM.

Materials and methods

Study participants

With the approval of institutional board, the prospectively maintained database from 2003 to 2017 was retrospectively reviewed. Patients with pathologically confirmed ccRCC-BM were identified. Their primary renal lesions or metastatic bone lesions were examined. Immunohistochemical (IHC) stain was performed in part of the bone lesion samples and results were reviewed as well. Patients whose clinical, pathological (including IHC stain results) profiles could not be found were excluded from the study.

Date collection

For each eligible ccRCC-BM patient, the following data were collected:

1) Clinical features: demographic characteristics (gender, age), time from the diagnosis of RCC to RCC-BM (Time to bone metastasis, TTBM), type of urological intervention and orthopedic metastasectomy, sites of bone metastasis, concomitant of visceral metastasis and existence of skeletal related events (SREs, including pathological fracture and spinal compression) [12] and information of local and systemic therapies performed.
2) Pathological features: expression of renal specific, targeted therapy related and prognosis related molecular biomarkers in bone lesion, including cytokeratin (CK), CK7, CK20, CD10, carbonic anhydrase (CA)-IX, epithelial membrane antigen (EMA), paired box gene (PAX)-8, PAX-2, vimentin, Ki-67, vascular endothelial growth factor (VEGF), platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFR), CD117, human epidermal growth factor receptor (Her) 2 (if records were applicable).
3) Patients' prognosis prediction and outcome profiles: MSKCC/Motzer score was selected for prognostic prediction since not all ccRCC-BM patients in this series received anti-VEGF agents. According to the scoring criteria [13], parameters including lactate dehydrogenase level (LDH, if greater than 210U/L), Karnofsky performance status (KPS, if less than 80%), hemoglobin level (if inferior to lower normal limit: 13.5 g/dL for male, 12.0 g/dL for female), calcium level (if greater than 2.5 mmol/L), time from diagnosis to start of systemic treatment (if less than 1 year) were collected at the point when bone metastasis was first diagnosed and before the beginning of therapies. When each criterion was met, 1 point would be scored. Patients with 0 points would be stratified to the favorable risk group. Patients with 1–2 points were set to the intermediate risk group. Patients with 3 or more points were set to the poor risk group.

The survival surveillance started right after the bone metastasis diagnosis. The primary endpoint was death in the follow-up. Then OS time was calculated.

Statistical analysis

Descriptive analysis were conducted for demographic data, tumor-specific data (bone metastasis sites, concomitant of visceral metastasis, TTBM, SREs and type of interventions), and pathological features (positive rates of selected biomarkers). Categorical variables were presented as numbers and percentages and continuous variables were presented as median and interquartile range. Kaplan-Meier survival analysis was used to calculate OS time.

Univariate analysis, such as one-way ANOVA test, Chi-square test and/or Fisher's exact test, along with multivariate logistic regression were carried out to figure out the possible relationships between prognosis prediction (MSKCC/Motzer score and risk stratification) and clinical, pathological features.

Those analyses were conducted using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA). A two-sided p value of less than 0.05 was considered to indicate statistical significance.

Results

Demographic, clinical and pathological characteristics: description

Within the time mentioned above, medical records of 106 mRCC patients with bone metastasis were reviewed. The median age of the series was 59 years old and 80.2% of patients were male (Table 1).

Nearly half (44.3%) of the enrolled ccRCC-BM patients had synchronous bone metastasis as their first bone metastases were diagnosed at the same time with their renal tumors. The commonest site of metastatic bone lesion was axial bone (vertebrate 46.2% and pelvis 38.7%), following by extremities (upper 18.9% and lower 19.8%). Flat bones, such as lib, sternum and skull were also found involved. No significant difference of site of bone metastasis was found between synchronous and metachronous metastasis groups (Table 2).

While persistent and intolerable pain was most frequently

Table 1
Patients' demographic and clinical features.

	Number of patients (n = 106)	%
Gender		
Male	85	80.2%
Female	21	19.8%
Age		
Median (Interquartile range)	59	(51,68)
TTBM		
Synchronous	47	44.3%
Metachronous	59	55.7%
Site of bone lesion		
Vertebrate	49	46.2%
Pelvis	41	38.7%
Upper extremities	20	18.9%
Lower extremities	21	19.8%
Lib	10	9.4%
Sternum	2	1.9%
Skull	5	4.7%
Concomitant of visceral metastasis		
Liver	6	5.7%
Lung	21	19.8%
Brain	1	0.9%
Gallbladder	1	0.9%
Contralateral adrenal	4	3.8%
Pleura	1	0.9%
Mediastinum	1	0.9%
Skeletal related events/SREs		
Pathological fracture	12	11.3%
Spinal cord compression	46	43.4%
Urological intervention		
Radical Nephrectomy	90	84.9%
Partial Nephrectomy	5	4.7%
Orthopedic metastasectomy		
En-bloc resection	38	35.8%
Intralesional resection	37	34.9%
Cytoreductive resection	31	29.2%

Table 2
Patients' clinical features (continued): stratification of site of bone metastasis according to the time of bone metastasis (synchronous vs metachronous).

Site of bone lesion	Synchronous (n = 47)	Metachronous (n = 59)	p value
Vertebrate	23 (48.9%)	26 (44.1%)	0.617
Pelvis	19 (40.4%)	22 (37.3%)	0.742
Upper extremities	12 (25.5%)	8 (13.6%)	0.118
Lower extremities	10 (21.3%)	11 (18.6%)	0.736

Table 3
Patients' pathological feature: IHC stain of bone lesions.

Characteristics	Positive/applicable stains	%
Biomarker		
CK	87/89	97.8%
CD10	77/85	90.6%
CA-IX	39/42	92.9%
EMA	19/21	90.5%
PAX-8	44/50	88.0%
PAX-2	20/20	100%
Vimentin	93/94	98.9%
VEGF	14/23	60.9%
PDGFR	18/23	78.3%
EGFR	23/23	100%
CD117	4/31	12.9%
Her2	2/23	8.7%
	Median index	Interquartile range
Ki-67	15%	(10%, 30%)

CA: carbonic anhydrase, CD: cluster of differentiation, CK: cytokeratin, EGFR: epidermal growth factor receptor, EMA: epithelial membrane antigen, Her: human epidermal growth factor receptor, PAX: paired box gene, PDGFR: platelet-derived growth factor receptor, VEGF: vascular endothelial growth factor.

complained by bone metastasis patients, more severe SREs, like pathologic fracture (11.3%) and spinal cord compression (43.4%), happened in more than half of all patients (Table 1). As spine-related events usually led to paralysis and/or immobilization, those patients' physical performance and life qualities were impaired.

For 28 patients (28.3%), bone was not the only metastatic organ during the disease course. Lung (19.8%) was the most detected site of concomitant metastasis (Table 1). Other abdominal organs, such as liver, gallbladder and contralateral adrenal were more likely to succumb to distant metastasis (10.4% in total). Besides, concomitant metastasis in brain, pleura and mediastinum were also recorded in several patients.

Nephrectomy was highly recommended the in management of ccRCC-BM. Ninety patients (84.9%) in this series received radical nephrectomy and 5 patients (4.7%) received partial nephrectomy. Bone metastasectomy was another crucial step for tumor control. Curative resection of bone lesions, including en-bloc and intralesional resection with marginal scraping, was performed in 70.7% patients. Cytoreductive resection with radiofrequency ablation was performed for the rest (Table 1). Systematic therapies, including the use of targeted medication (23 patients, 21.7%), immunotherapy (interferon and interleukin, 18 patients, 17.0%), bisphosphonate agent (9 patients, 8.5%), and local radiotherapy (11 patients, 10.4%) were also found in this series.

Samples of bone lesions were obtained from all 106 patients and exanimated by experienced pathologists. Since lesions in metastasis sites might present dedifferentiated morphological feature under light microscopy, IHC staining was needed to determine the origins and specific histopathological sub-types. Certain kinds of diagnostic biomarkers were selected to verify ccRCC-BM [14–21]. CK, PAX-8, PAX-2, vimentin, CA-IX, EMA and CD10 had relatively higher positive expression, while expression of CK7, CK20 and CD117 was low (Table 3). Meanwhile, expression of VEGF and PDGFR were examined as potential systemic therapeutic targets. The positive rates were around 60–80% (Table 3) in IHC staining. Nearly all applicable samples staining with EGFR had the positive expression (100%). The median of Ki-67, a proliferation index, was 15% in those bone lesions.

Prognosis prediction and outcome analysis

Using variables at first diagnoses of bone metastasis to calculate MSKCC/Motzer score, those patients were stratified into different risk groups (Table 4). The majority of patients had intermediate (n = 67, 63.2%) and poor (n = 20, 18.9%) prognosis.

The consequent Kaplan-Meier survival analysis indicated that in

Table 4
Risk stratification based on MSKCC/Motzer score and the relationship between prognosis prediction and clinical, pathological features.

Characteristics (below)/Risk stratification (right) (n = 106)	Favorable (n = 19, 17.9%)	Intermediate (n = 67, 63.2%)	Poor (n = 20, 18.9%)	P value
Gender (male)	16	55	14	0.473
Age (Mean)	57.42	59.40	62.95	0.383
TTBM (Synchronous/Metachronous)	1/18	34/33	12/8	<0.001
Site of bone lesion				
Vertebrate	6	32	11	0.313
Pelvis	8	26	7	0.882
Upper extremities	6	13	1	0.100
Lower extremities	2	15	4	0.602
Lib	1	7	2	0.898
Sternum	0	2	0	1.000
Skull	2	2	1	0.181
Concomitant of visceral metastasis	3	16	9	0.097
SRE	10	33	15	0.125
Pathological fracture	3	6	3	0.496
Spinal cord compression	7	27	12	0.269
Biomarker (positive rates)				
CD10	15/16	47/53	15/16	1.000
CA-IX	6/6	27/28	6/8	0.137
PAX-8	7/8	30/35	7/7	0.815
VEGF	2/3	8/15	4/5	0.816
PDGFR	3/3	11/15	4/5	1.00
CD117	1/5	1/18	2/8	0.235
Ki-67	10.00%	18.53%	20.00%	0.787

CA: carbonic anhydrase, CD: cluster of differentiation, PAX: paired box gene, PDGFR: platelet-derived growth factor receptor, SREs: skeletal related events, TTBM: time to bone metastasis, VEGF: vascular endothelial growth factor.

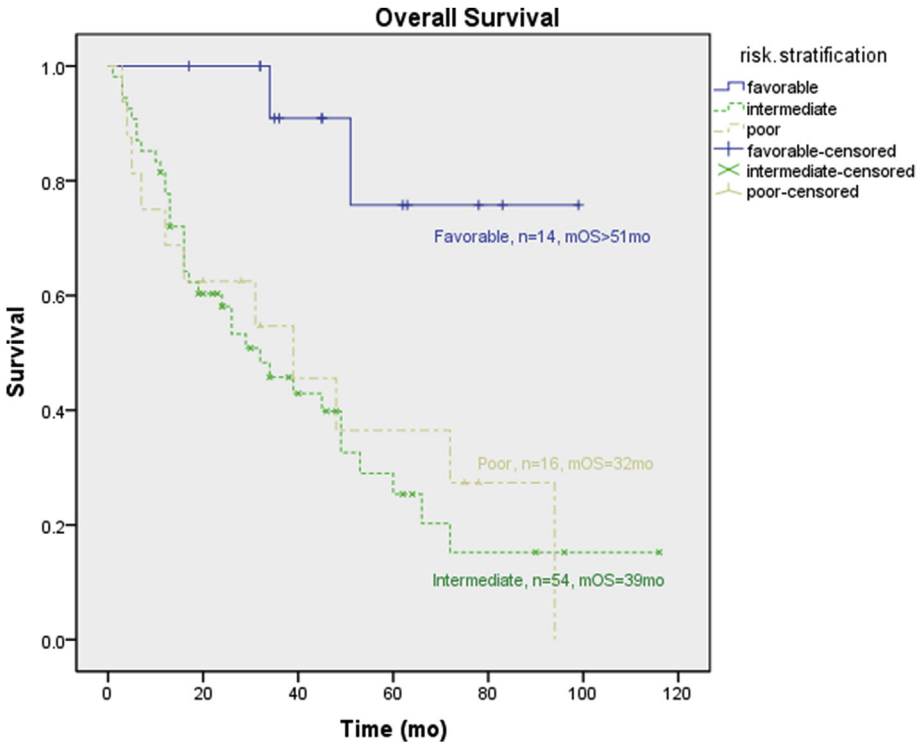

Fig. 1. Survival curves for MSKCC/Motzer prognosis risk group, Plotting the Time (months) Since first orthopedic procedure (X-Axis) against the proportion of overall survival (Y-Axis). 22 Patients were excluded from analysis since no follow-up records could be found.

the median follow up time of 29.5 months (interquartile range 13–48.75 mo), the median OS (mOS) time of those ccRCC-BM patients was 45 months. Survival curves for MSKCC/Motzer prognosis risk group were shown in Fig. 1. There was significant difference in the survival profiles among three MSKCC/Motzer risk groups (Fig. 1; $p < 0.01$). The mOS was significantly longer (>51 mo) in the favorable-risk patients ($n = 14$) than those in the intermediate risk group (32 mo, $n = 54$), and poor risk group (39 mo, $n = 16$). No significant evidence was found between intermediate and poor risk groups ($p = 0.757$).

In relevant analysis, patients with synchronous bone metastasis (TTBM = 0) had worse prognosis (<0.001) comparing to those with metachronous metastasis (TTBM>0) in univariate analysis. The multivariate logistic regression analysis, in which confounding factors were well balanced, indicated that not only shorter TTBM [odds ratio (OR) 1.019, 95% Confidence interval (CI) (1.007, 1.031)], but also elderly age [OR 1.040, 95% CI (1.001, 1.080)] and concomitant of visceral metastasis [OR 3.883, 95% CI (1.375, 10.967)] were associated with unfavorable prognosis (Fig. 2). Metastasis to upper extremities (including bone in shoulder, upper arm and forearm) had a mere tendency of poor prognosis.

As for the selected biomarkers in the current pathological dataset, the univariate analysis failed to suggest any expression difference among different risk groups. After gender, age, site of bone metastasis were separated balanced for each biomarker, positive CA-IX expression was ascertained to be a correlative factor [OR 0.017, 95% CI (0.001, 0.377)] (Fig. 3) as expression loss ("CA-IX escape") was associated with worse prognosis. Those biomarkers related tumor growth and invasion, such as VEGF, EGFR and PDGFR, spread evenly among different risk categories.

Discussion

The emergence bone metastasis in RCC patients always indicates advanced disease stage. For a long time, the treatments for RCC-BM were aimed at palliation. The median survival time of ccRCC-BM was usually below 24 months. The osteolytic property of ccRCC-BM makes it more hazardous since the occurrence of SREs would further increase mortality and reduce the median survival time [2,22]. Genetic and histological heterogeneity among the broad spectrum of RCC sub-types also hindered the understanding of their malignant behaviors. Studies of RCC-BM were not immune.

Bone scan, a conventional whole-skeleton assessment of bone metastases, was widely used in this ccRCC-BM series [23]. As it was recommended in the presence of specific clinical signs and symptoms [24], several patients were also diagnosed by local computed tomography (CT) and magnetic resonance imaging (MRI). It should be noted that all patients in the series were offered locally surgical intervention for bone lesions. Few comparable ccRCC-BM series like this could be found.

Previous findings have suggested that MSKCC/Motzer score system could sensitively distinguish mRCC patients' prognosis [13,25]. Kaplan-Meier analysis performed in this study suggested less risk-stratification categories were required in ccRCC-BM specific prognosis prediction system as patients in intermediate and poor risk groups had similar outcomes.

The 4:1 male predominance in this ccRCC-BM series was much higher than those in general RCC population (1.5:1 male predominance) or in ccRCC population (2.8:1 male predominance) [24,26]. The "gender bias" phenomenon in advanced ccRCC, especially in hematogenous metastasis of ccRCC, has been noticed before and attributed to the expression of androgen receptor (AR). Using ccRCC lung metastasis subjects, the study has shown that AR might function through positively regulating the expression of VEGF-A, promoting the growth of vascular endothelial cells and leading to the hematogenous tropism in invasion and metastasis. The expression of AR could also be assumed as bone metastasis determinant in ccRCC but further demonstrations are needed.

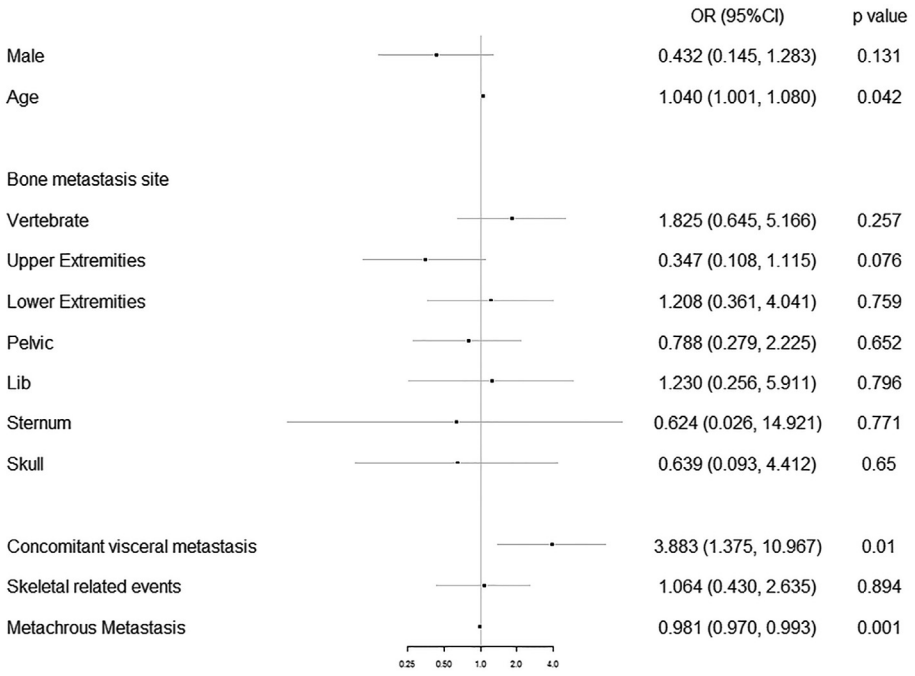

Fig. 2. Association between unfavorable prognosis and clinical features of ccRCC-BM patients. Clinical features included demographic and tumor-specific characteristics and logistic regression analysis was used.

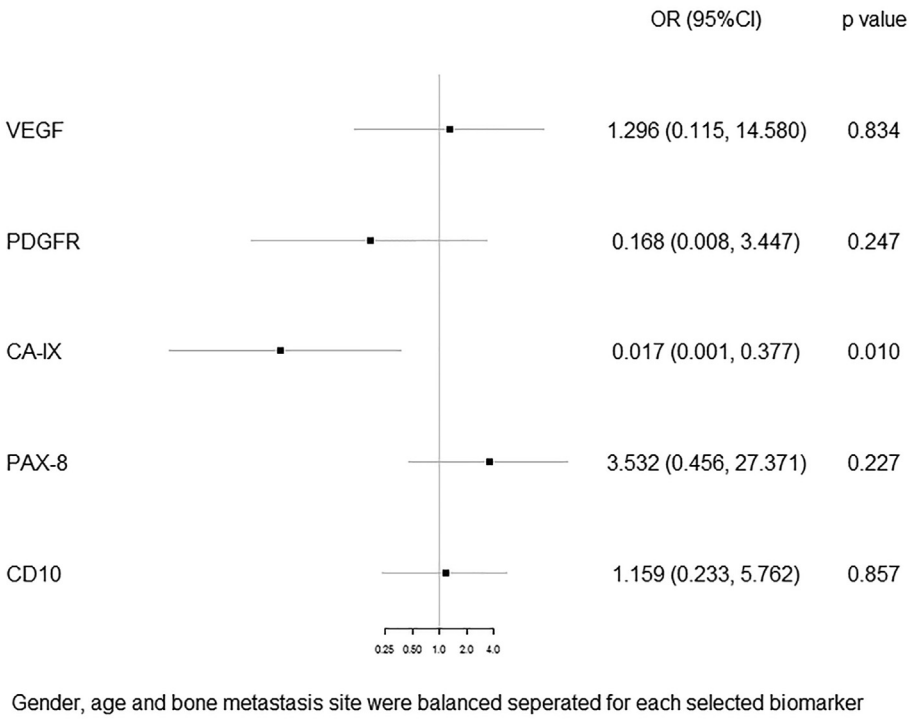

Fig. 3. Association between unfavorable prognosis and expression of selected biomarkers in metastatic bone lesion. Using logistic regression analysis, confounding factors were balanced separately for each biomarker.

Recent consensus recommended the use of multimodal management strategy, in which wide resection of lesions, radiotherapy, systemic therapy were included [27]. In this center, metastasectomy of bone lesion, accompanied by those strategies for tumor control (Fig. 4), has been demonstrated to significantly improve ccRCC-BM patients' mOS (45 mo) comparing to those (less than 24 mo) reported previously [2]. Richer blood supply and closeness to the primary site made axial bone (vertebrate and pelvis) the most frequent site for bone metastases. These kinds of lesion, particularly multiple lesions in vertebral columns, increase the risk of skeletal instability. Besides, pathological fractures in extremities impair patients' autonomy and independence. Those

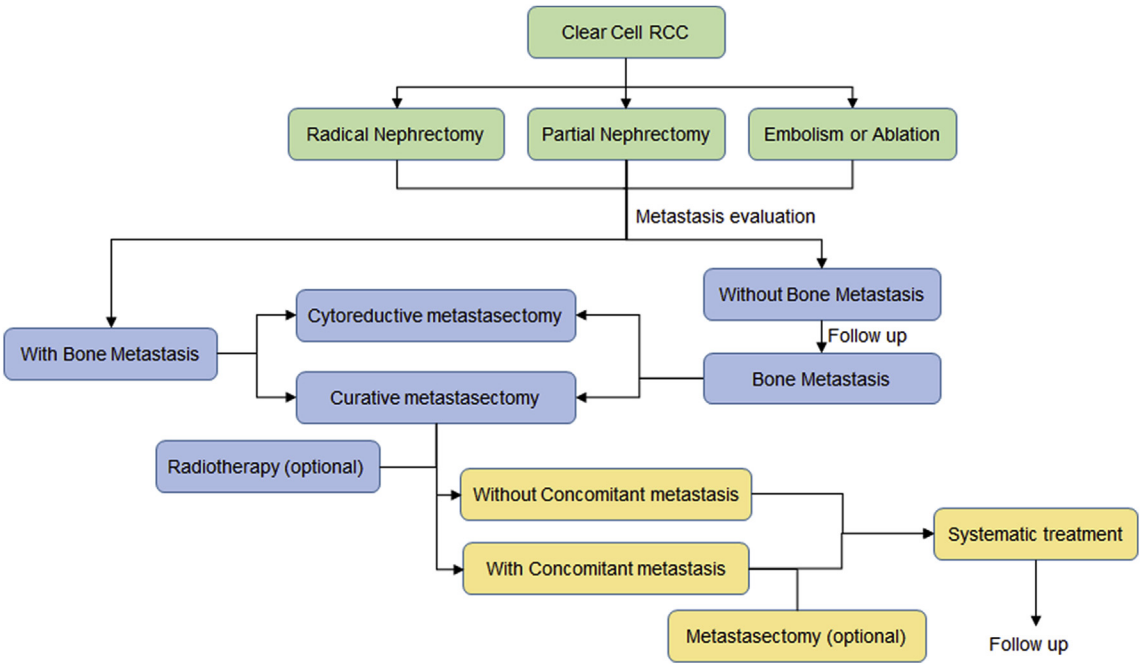

Fig. 4. Flow chart of ccRCC-BM management in this center.

urge the need for orthopedic procedures. Younger population with the mean age under 60 years old, found in this series, were more likely to receive such curable procedures considering the possible huge blood loss. By contrast, patients with elderly age, who had poorer physical performance and more vulnerable cardiopulmonary function capacity, were intolerant for complicated surgical treatments and were still at risk of worse outcome.

Several cutting-edge agents, including cabozantinib (tyrosine kinase inhibitors/TKI of c-Met and VEGFR2), nivolumab (anti-Programmed cell death protein/PD-1 monoclonal antibody) and ipilimumab (anti-cytotoxic T-lymphocyte-associated protein/CTLA-4 monoclonal antibody) [9] have been nominated in latest guideline. But the mainstream of systemic therapy for treatment-naïve metastatic ccRCC patients in this center remains the use of sunitinib, the TKI of both VEGFR and PDGFR [28]. Zoledronic acid agents and denosumab (anti-Receptor Activator for Nuclear Factor-κ B Ligand/RANKL monoclonal antibody) are additionally recommended [29]. However, the response rate (RR) of sunitinib was only 35% for ccRCC-BM patients in previous study [30]. The positive rates of VEGF and PDGFR detected in metastatic bone lesions were much higher than that. The role of VEGF and PDGF in bone metastasis of ccRCC could be overestimated. It is not reliable to use the IHC stain results only in the decision making for targeted agents and stain of these factors is still not prioritized in routine practice.

In the applicable ccRCC-BM samples, “CA-IX escape” was found in bone lesions to associate with worse prognosis. CA-IX has been long regarded as a prominent marker in several tumors due to its prompt response to hypoxia during tumorigenesis. In ccRCC, the over expression of CA-IX is related to good prognosis and decreased positivity has been observed in diseases with higher tumor stage [31,32]. Together with this biomarker, multiple-organ involvement and synchronous metastasis [2,33] were determined to be correlative factors for poorer prognosis and further introduction to prediction system could be considered.

The limitations of this work include the missing of the stage, grade characteristics in primary RCC lesions. Additionally, histopathological data of primary RCC lesions are missing. More comprehensive analysis should be potentially developed. As the IHC stain results for diagnostic and prognostic biomarkers were not applicable from all enrolled patients, effects could be overrated. Data from patients lost to follow-up contributes to another confounding factor.

Conclusion

Male and middle-aged prominence was the feature of ccRCC-BM patients, while more lesions were found in axial bones. The outcome of ccRCC-BM remained poor for patients with intermediate and high risk using MSKCC/Motzer score and risk stratification. Resection of bone lesions accompanied by systematic therapy for selected patients could improve their outcomes.

Shorter TTBM, elderly age, concomitant multi-organ metastasis and the expression loss of CA-IX were correlated with the poor overall outcome. Along with gender-bias, feasibility for surgical treatment, those factors are suggested to be incorporated into modified ccRCC-BM specific prognosis prediction system.

Declarations of interest

None.

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