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Original Research

Prognosis of renal cell carcinoma with bone metastases: Experience from a large cancer centre

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Abstract ***Background:*** Bone metastases (BMs) are associated with significant morbidity and shorter survival in renal cell carcinoma (RCC). Our purpose was to identify prognostic factors for overall survival (OS) in RCC patients with BMs.
Methods: Data from patients with BMs from RCC treated at Gustave Roussy between April 1992 and March 2016 were retrospectively collected. Age, sex, Eastern Cooperative Oncology Group-Performance Status, Memorial Sloan-Kettering Cancer Center (MSKCC) risk groups, histology, number and site of bone lesions, concomitant metastases (presence and sites), therapy for BMs (radical resection or palliative surgery, radiotherapy and other local and systemic treatments) and time from diagnosis to BMs were analysed. Synchronous solitary bone metastasis (SSBM) was defined as a single BM without concomitant visceral lesions at the initial diagnosis of RCC. OS was calculated from the date of BMs diagnosis to death or last follow-up using Kaplan–Maier method and modelled with Cox regression analysis.
Results: From 1750 patients with diagnosis of RCC followed at Gustave Roussy Cancer Campus, 300 patients with BMs were identified. Median time from diagnosis to BMs was 32.4 months (range 0–324 months). In 64 patients (21%), bone was the only metastatic site, and 22 patients (7%) had an SSBM and 236 patients (79%) had concomitant metastases in other sites. Median OS was 23.2 months (95% confidence interval 19.9–26.2). SSBM patients had better OS than those with concomitant metastases (40 vs 20 months; $P < 0.001$). At

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multivariate analysis, concomitant metastases remained predictor of poor prognosis, while MSKCC risk group, radical resection and SSBM were predictors of better OS.
Conclusions: This study suggests that MSKCC score, numbers of BMs and radical resection are important prognostic factors for RCC patients with BMs. Additionally, in the presence of solitary BM without concomitant metastases at the initial diagnosis of RCC, bone surgery should be considered to achieve local tumour control and likely increase OS.

1. Introduction

Bone metastases (BMs) are a common site of relapse in many types of solid cancers, including kidney cancer [1,2]. In metastatic renal cell carcinoma (mRCC), BMs are a very frequent site of disease, occurring in almost 30% of patients [3].

BMs from RCC are predominantly osteolytic and are associated with high rates of skeletal-related events (SRE) defined as a pathological fracture, surgical intervention, requirement for palliative radiotherapy to bone, spinal cord compression or hypercalcemia [4,5]. Almost 70% of RCC patients with BMs will experience at least one SRE, inducing impairment of quality of life [2].

The efficacy of targeted agents in BMs is difficult to fully assess. First, BMs being mostly non-measurable lesions by RECIST criteria, the bone response to treatment has not been evaluated in pivotal clinical trials [6]. Second, patients with BMs only are usually excluded from clinical trials, considering the lack of measurable disease. In addition, BMs are usually related to a more aggressive subtype of disease [7].

BMs have been identified as an independent prognostic variable associated with poor survival in patients with mRCC [7–9]. An analysis by the International Kidney Cancer Working Group identified bone or liver metastases treated with targeted therapy as conferring significantly poorer overall survival (OS) than other metastatic sites, with a hazard ratio for BMs of 1.4 (95% confidence interval [CI], 1.22–1.62) [10]. However, the occurrence of patients with BMs from RCC with long survival is not infrequent [11–13]. A possible explanation includes data on tumour heterogeneity and molecular mechanisms involved in RCC growth and metastatic spread [11,14]. Understanding the prognostic impact of BMs is critical to better personalise treatment decisions in patients with mRCC, especially in terms of local treatment. The aim of this study was to investigate the prognostic role of BMs in a large cohort of patients with mRCC through stratification by patients' characteristics, cancer's characteristics, BMs' characteristics and treatments.

2. Patients and methods

This is a retrospective, observational, study of patients treated at Gustave Roussy Cancer Campus (GRCC) from 1992 to 2016 for mRCC. All patients with a radiological diagnosis of BMs from RCC have been assessed for eligibility between December 2015 and October 2016. All patients, with a histopathologic diagnosis of RCC and at least one BM (radiologically confirmed) during the course of disease, who received treatments according to treating physician's practice were included, as long as follow-up visits were available. Patients with a unique visit at GRCC for the second opinion have been excluded.

Patient' characteristics, treatments and outcome data were retrospectively collected from electronic medical records, including demographic data (age and sex), patients' characteristics (MSKCC risk score, performance status [PS] according to the Eastern Cooperative Oncology Group scale and presence of bone pain), cancer's characteristics (nephrectomy, histological subtype, primary tumor site, regional lymph node involvement, presence of distant metastatic spread (TNM) staging, Fuhrman's grade and visceral metastases concomitant with BMs), BMs' characteristics (number, site and time to BMs [TTBM]), BMs' treatments and SRE. Diagnosis of BMs was radiological, mostly with contrast-enhanced computed tomography (CT) or with magnetic resonance imaging. Other metastatic sites (liver, lung, lymph nodes and other) were defined with total body contrast-enhanced CT. Patients' characteristics were collected at the time of diagnosis of metastatic RCC and, in case of not synchronous BMs, at the time of diagnosis of BMs. Synchronous solitary bone metastasis (SSBM) was defined as a single BM without concomitant visceral lesions within 60 d from the time of diagnosis of the primary RCC. TTBM was recorded as time between diagnosis of RCC and time of occurrence of first BM. OS was measured from BMs to the last event (death/last follow-up).

Descriptive statistics were used for patient demographics, patient's and disease's characteristics and incidence of SREs. Kaplan–Meier method and Mantel–Haenszel log-rank test was used to compare survival among groups. A Cox regression model was applied to the data with a univariate and multivariate approach. Variables not fitting at univariate regression analysis were excluded for the multivariate model. All significance levels were set at a 0.05 value. MedCalc software (version 16.8.4) and GraphPad Prism software (version 7) were used for statistical analyses.

3. Results

From 1750 patients with diagnosis of RCC followed at GRCC between April 1992 and March 2016, BMs were confirmed in 300 patients (17%). Eighty additional patients were excluded for a unique visit to GRCC. Median age at the diagnosis of BMs was 59 years (range: 19–83 years), with a majority of men (77% vs 23% for women). The most common histological subtype was clear-cell RCC (258 patients; 86%), followed by papillary (25 patients; 8.3%), chromophobe (nine patients) and other histologies (eight patients). Prognostic group using MSKCC criteria was good in 31 (10%), intermediate in 198 (66%) and poor in 71 patients (24%). Baseline patients' characteristics are shown in Table 1.

Seventy-three patients (24%) had solitary or multiple synchronous BMs, and the majority of the patients (227, 76%) developed BMs during the course of the disease. With regards to the number of BMs, 170 patients (57%) had initially a unique BM, 109 (36%) had two to five BMs and 21 (7%) had more than 5 BMs. In terms of location of BM, the spinal column was involved in 177 patients (59%), the sacrum in 116 (39%) and the long bones in 94 (31%). In 64 patients (21%), bone was the only metastatic site. In particular, 22 of them (7%) had an SSBM. Conversely, 236 patients (79%) had concomitant visceral metastases (59% lung, 37% lymph nodes, 17% liver and 24% other). The characteristics of BMs are shown in Table 2.

With a median follow-up of 30 months and 253 (84%) deaths, median OS was 23.2 months from the diagnosis of BMs (Fig. 1). Median TTBM was 32.4 months (range 0–324 months). Median times to first and second SRE were 5.3 months (range 0–46 months) and 10.8 months (range 0–73 months), respectively. More than 56% of the patients experienced at least one SRE.

To note, OS was not associated with Fuhrman grade in the univariate analysis. Clear-cell histology was associated with a longer survival as compared with other histological subtypes (24.1 vs 17.6 months, $P < 0.0033$). The median OS was 42.7, 22.3 and 7.2 months in patients with good, intermediate and poor prognosis, respectively ($P < 0.001$).

Patients with a solitary bone lesion had a longer survival than patients with multiple BMs (27.7, 18.2 and 9.2 months in patients with one, two to five and more than 5 BMs, respectively, $P < 0.0001$). Moreover, the location of BMs had an impact on OS: patients presenting with BMs located to long bones had a better prognosis than patients with BMs located to spinal column or sacrum (28.6 vs 19.7 vs 17.6 months, respectively, $P < 0.005$). Significant differences in terms of OS were found when comparing patients presenting with concomitant visceral and lymph nodal metastases with those with only bone as the unique site of metastatic disease (17.6 vs 46.4 months, respectively, $P < 0.0001$). The site of concomitant metastases (lung, liver, lymph nodes and other) was not significantly associated with OS ($P = 0.40$). When comparing patients with synchronous BMs versus metachronous, no significant difference in terms of OS was found. It should be noted that patients with synchronous BMs had less concomitant visceral metastases than metachronous BMs (68% vs 86%, $P = 0.0025$, respectively). In addition, patients with synchronous BMs have been treated more frequently with radical surgery compared to patients with metachronous BMs (54% vs 34%, $P = 0.0044$, respectively). Kaplan–Meyer plots of OS are shown in Fig. 2.

Table 1
Baseline patient's characteristics.

Variable	Patients, n (%), (N = 300)
Median age, y (range)	59 (19–83)
Sex	
Male	230 (77)
Female	70 (23)
Tumour histology	
Clear cell	258 (86)
Other	42 (14)
ECOG-Performance Status >2	51 (17)
MSKCC criteria	
Good	31 (10)
Intermediate	198 (66)
Poor	71 (24)
Fuhrman grade	
2	67 (22)
3	113 (38)
4	44 (15)
NA	76 (25)
Presence of concomitant metastases	236 (79)
Sites of concomitant metastases	
Lung	177 (59)
Lymph node	112 (37)
Liver	50 (17)
Other	71 (24)

ECOG = Eastern Cooperative Oncology Group; MSKCC = Memorial Sloan-Kettering Cancer Center.

Table 2
Characteristics of bone metastases.

Variable	Patients, n (%) (N = 300)
Number of BMs	
1	170 (57)
2–5	109 (36)
>5	21 (7)
Location of lesions	
Spinal column	177 (59)
Sacrum	116 (39)
Long bones	94 (31)
Synchronous BMs	73 (24)
Single synchronous BMs	22 (7)
Bone pain	
Yes	225 (75)
No	75 (25)
SRE	
Yes	168 (56)
No	132 (44)

BMs = bone metastases; SRE = skeletal-related events.

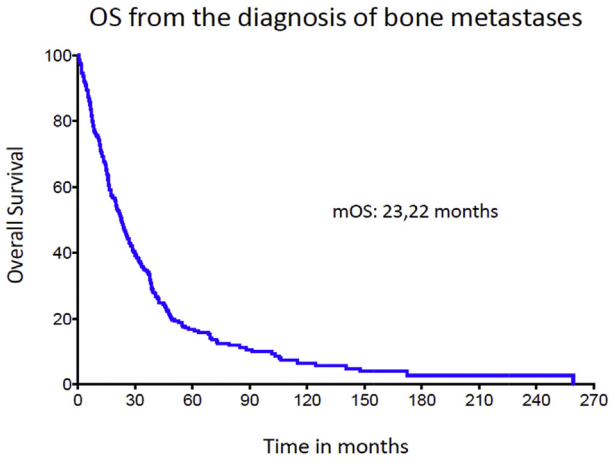

Fig. 1. Kaplan–Meyer plot of overall survival from the diagnosis of bone metastases. OS, overall survival.

In the multivariate analysis, risk score according to MSKCC was associated with OS ($P < 0.05$). In addition, concomitant visceral metastases remained predictor of worse outcome ($P < 0.05$). Patients with an SSBM were characterised with a longer OS than those presenting with concomitant metastases (40 vs 20 months, $P < 0.001$). Regarding BMs' therapy, radical resection was associated with a longer survival ($P < 0.05$), while no correlation with OS was found for palliative surgery, radiotherapy and the other local and systemic treatments (Table 3).

4. Discussion

To our knowledge, this is the largest monocentric study to investigate the natural history of BMs in patients with mRCC. Among mRCC patients, approximately one-third will develop BMs, representing the second most common site of disease (after lung) in advanced RCC [3,9]. The probability to develop BMs in RCC patients has increased with the introduction of new therapies and prolonged survival. BMs were confirmed in approximately 17% of our mRCC database, which is lower than other reported incidence of BMs. Only patients with at least one BM were included in our study, and several patients with a single visit for the second opinion were not analysed. The reason for lower incidence of BMs in our series is likely due to a selection bias of patients referred to our institution for therapy, especially in the cytokines era. At that time, patients with poor PS were mostly treated with palliative care outside of GRCC. BMs have been identified as an independent prognostic variable associated with poor survival in patients with mRCC. Median OS after diagnosis of BMs in our study is 23.2 months, consistent with previously reported data [3,9,15]. As described before, non-clear cell histology and MSKCC risk group were significantly associated with worse prognosis [7,9,16]. At the multivariate analysis, risk group according to MSKCC remained predictor of OS in our cohort. No significant difference was found in our series between synchronous and metachronous BMs. Although surprising, this finding is consistent with a previous study from Santoni *et al.*, [7] who analysed the records of 398 patients with BMs from 19 centres, reporting no significant difference between synchronous and metachronous BMs. The statistically significant lower rate of concomitant (visceral and lymph nodal) metastases and the higher rate of radical surgery in the group of synchronous BMs could partially explain this singular result. Regarding different sites of BMs, in agreement with literature data [9,17], 31% of patients in our cohort had metastases in their long bones, while the axial skeleton was involved in the majority of patients. Interestingly, patients with metastases localised to long bones were characterised by a better prognosis. A possible explication for the favourable prognosis of patients with peripheral location of BMs could be the possibility to undergo a radical surgery.

We also reported the incidence and prognostic role of concomitant visceral metastases. The association between bone disease and other metastases confers poor prognosis, as already suggested [7,18]. However, surprisingly compared with other series, presence of concomitant liver metastases was not an independent prognostic factor in our series [10,18,19]. This is, however, in accordance with Santoni's series, in which the presence of liver metastases was not an independent prognostic factor [7].

The majority of patients with BMs may experience extremely debilitating skeletal complications (i.e. SRE, 56% of patients in this study) and that will deeply impact their quality of life [20]. The rate of SRE in our study is consistent with previously reported rates (60–74%) [15].

With regards to the number of BMs, single BM is associated with a better prognosis than multiple metastases [7,9]. However, the most interesting result of our study concerns the SSBMs. Between synchronous and metachronous BMs, there was no significant difference in OS but if the BM is solitary and synchronous is characterised by a better prognosis. Improved survival in this group of patients may have different explanations, including lower tumour burden, a different biology, but mostly the opportunity to perform a radical resection. Indeed, the large majority of patients with an SSBM underwent a bone surgery (76%) and radical resection was an independent prognostic factor associated with longer survival. These data are even more interesting if we consider that studies on management of solitary BMs are limited. No prospective trials or large retrospective analyses on the outcome of different local treatment options (surgery, radiotherapy, cryotherapy, radiofrequency and vertebroplasty) have been reported, and there are no standard recommendations on the best treatment modality to use in this group of patients. Small retrospective data and case reports suggest that

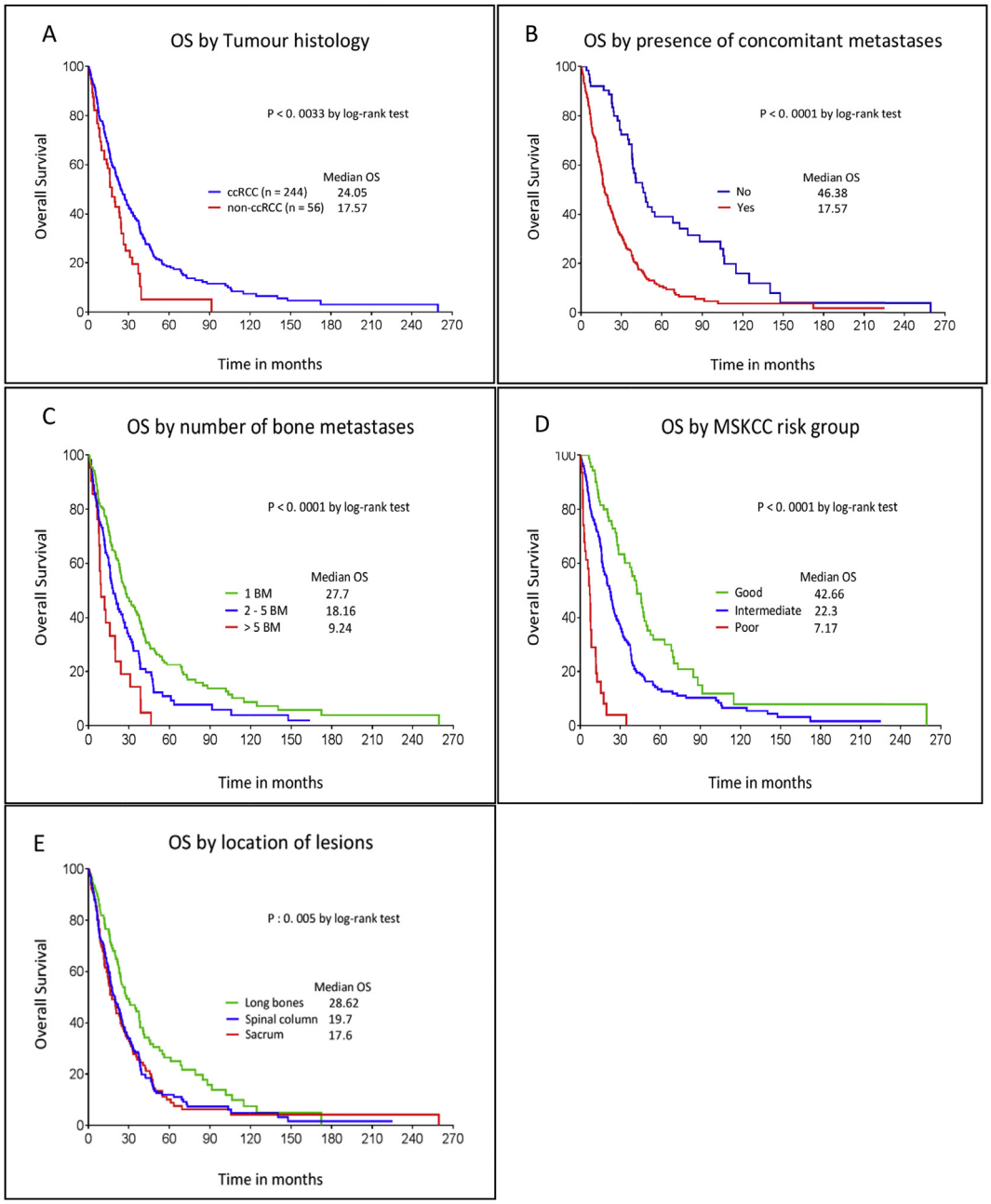

Fig. 2. Kaplan–Meyer plots of overall survival by number of (A) bone metastases, (B) tumour histology, (C) concomitant metastases, (D) MSKCC risk group, and (E) location of lesions. OS, overall survival; MSKCC, Memorial Sloan-Kettering Cancer Center.

patients with a solitary metastasis are candidates for wide resections, and if the resection is complete, the prognosis of these patients is more favourable [21–24]. Obviously, accessibility and resectability of metastases, patients' PS and presence of comorbidities should be considered before radical surgery. Cryotherapy, radiofrequency and radiotherapy modalities (conventional or stereotactic body radiotherapy) can provide a valid local non-invasive treatment alternative to surgery, with results similar to the rates of surgical resection [25–27]. However, in our series, local treatments were not significantly associated with improved OS may be because of the paucity of data, considering that bone resection is traditionally the strategy of choice for the management of solitary BMs.

Finally, our series was not aimed to analyse the role of medical treatment. Thus, the impact of targeted therapy in our series is difficult to assess. Data on the outcomes of mRCC patients with BMs treated with TKIs are limited but have suggested worse outcomes compared with those without BMs [9]. Whether TKIs treatment have improved the OS of patients with mRCC with BMs is still an open question. Recent studies testing MET inhibitors in prostate cancer and other cancers

Table 3
Multivariate analysis for overall survival from the diagnosis of BMs.

Covariate	HR	*P*	95% CI
Histology (CC vs NCC)	1.17	0.36	0.82–1.68
MSKCC group	0.5	**<0.05**	0.38–0.67
Nephrectomy (yes/no)	0.74	0.10	0.50–1.07
Number of BMs (single/multiple)	1.09	0.61	0.77–1.52
Location of BMs (rachis/pelvis)	1.14	0.42	0.82–1.56
Single synchronous BMs (yes/no)	0.66	**0.04**	0.43–0.99
Visceral synchronous metastases (yes/no)	2.02	**<0.05**	1.39–2.96
Multiple treatments (yes/no)	0.98	0.89	0.72–1.32
BMs surgery (yes/no)	0.68	**0.01**	0.50–0.93
First treatment for BMs (surgery/RT)	0.84	0.35	0.57–1.21

BMs = bone metastases; CC = clear cell; CI = confidence interval; HR = hazard ratio; NCC = non-clear cell; P = p-value of significance; RT = radiotherapy.
P-value significance < 0.05.

demonstrated dramatically decreased bone scan uptake in patients after treatment [28]. Furthermore, emerging data suggest that MET inhibition might have clinical benefit in patients with mRCC, probably predominantly in patients with papillary RCC who have amplification of, or activating mutations in, MET. Cabozantinib is a small molecule inhibitor of MET, VEGFR2 and AXL receptors. In the subgroup analysis of the METEOR (cabozantinib vs everolimus in advanced RCC) trial, the HR for OS was 0.54 (95% CI 0.34–0.84) for patients with BMs [29,30], suggesting that cabozantinib could represent a good treatment option. The main limitations of our study are due to the retrospective design, as well as the changes in imaging modalities to detect BMs and in therapy management from 1992 until recently. Nevertheless, the monocentric aspect of this study with the majority of patients being treated by the same physician (BE) over time is very informative. In conclusion, our study suggests that for RCC patients developing BMs, MSKCC score, number of BMs at the initial diagnosis of RCC (1 vs >1) and radical resection are independent prognostic factors in mRCC. Based on these, radical surgery needs to be performed in patients with isolated BM to achieve local tumour control to delay the systemic treatments and to improve survival. As expected, the presence of BMs in association with other visceral disease confers a poor prognosis, with impaired quality of life due to a high incidence of SRE. Subsequently, in the era of multimodal therapy, palliative bone surgery or palliative local bone treatments should be considered to decrease SREs. The role of targeted agents as well as bone-targeted therapies remains to be determined [31]. Certainly, we need further improvement in treatment modalities to cure BM thereby decreasing morbidity and mortality.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.10.023.

Conflict of interest statement

The authors indicated no potential conflicts of interest.

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