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Impact of Bone and Liver Metastases on Patients with Renal Cell Carcinoma Treated with Targeted Therapy

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Abstract

Background: The skeleton and liver are frequently involved sites of metastasis in patients with metastatic renal cell carcinoma (RCC).
Objective: To analyze outcomes based on the presence of bone metastases (BMs) and/or liver metastases (LMs) in patients with RCC treated with targeted therapy.
Design, setting, and participants: We conducted a review from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) of 2027 patients with metastatic RCC.
Outcome measurements and statistical analysis: We analyzed the impact of the site of metastasis on overall survival (OS) and time-to-treatment failure. Statistical analyses were performed using multivariable Cox regression.
Results and limitations: The presence of BMs was 34% overall, and when stratified by IMDC risk groups was 27%, 33%, and 43% in the favorable-, intermediate-, and poor-risk groups, respectively ($p < 0.001$). The presence of LMs was 19% overall and higher in the poor-risk patients (23%) compared with the favorable- or intermediate-risk groups (17%) ($p = 0.003$). When patients were classified into four groups based on the presence of BMs and/or LMs, the hazard ratio, adjusted for IMDC risk factors, was 1.4 (95% confidence interval [CI], 1.22–1.62) for BMs, 1.42 (95% CI, 1.17–1.73) for LMs, and 1.82 (95% CI, 1.47–2.26) for both BMs and LMs compared with other metastatic sites ($p < 0.0001$). The prediction model performance for OS was significantly improved when BMs and LMs were added to the IMDC prognostic model (likelihood ratio test $p < 0.0001$). Data in this analysis were collected retrospectively.
Conclusions: The presence of BMs and LMs in patients treated with targeted agents has a negative impact on survival. Patients with BMs and/or LMs may benefit from earlier inclusion on clinical trials of novel agents or combination-based therapies.

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1. Introduction

The most common site of metastasis in patients with renal cell carcinoma (RCC) is the lung, affecting 45–50% of patients with metastatic disease [1]. Other frequent sites of involvement include the skeleton and liver, with estimates of involvement of 30% and 20%, respectively [1]. Bone metastases (BMs) from RCC cause significant morbidity and are associated with high rates of skeletal complications. Prior to the era of targeted therapy, the rate of skeletal-related events (SREs), defined as pathologic fracture, bone radiotherapy, bone surgery, spinal cord compression, and in some series hypercalcemia, was 74% to upward of 85% [2].

Recent advances in our understanding of the pathogenesis of RCC have led to a new treatment paradigm for patients with metastatic RCC. Although studies of patients treated in the cytokine era suggest that the presence of BMs and/or liver metastases (LMs) is associated with a poor prognosis, the impact of BMs and/or LMs on the outcomes of patients treated with agents targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) axis is largely unknown. We used the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) to determine whether baseline BMs and/or LMs are associated with worse overall survival (OS) and time-to-treatment failure (TTF) in patients with metastatic RCC treated with first-line targeted therapy.

2. Patients and methods

2.1. Study design

The IMDC is a consecutive patient series from institutions in Canada, Denmark, South Korea, and the United States. We used the IMDC to identify 2370 patients from 20 centers treated for metastatic RCC. The database was locked for the current analysis on October 10, 2012. Patient inclusion criteria comprised a diagnosis of metastatic RCC of any histologic subtype treated with first-line targeted therapy. Patients who received prior immunotherapy were included in the analysis. Patients were excluded from the analysis if they had missing information regarding baseline number of sites of metastasis, BMs, LMs, or choice of therapy. For this study, we included 2027 patients of all ages with metastatic RCC who received first-line targeted therapy between April 7, 2003, and August 8, 2012.

We retrospectively collected baseline demographic, clinical, and laboratory data, including those previously found to have prognostic value, on all patients using uniform database templates to ensure consistent data collection [3]. Laboratory values were standardized against institutional upper limits of normal and lower limits of normal values. We collected survival data from patient medical records or publicly available records. Institutional review board approval was obtained from each participating center.

2.2. Statistical methods

The primary outcome of this study was OS, which was defined as the time from initiation of first-line targeted therapy to death from any cause or was censored at the date of last follow-up. The secondary outcome was TTF, which was defined as the time from initiation of first-line targeted therapy to date of progression, drug discontinuation, death, or was censored at last follow-up. Distributions of OS and TTF were calculated using the Kaplan-Meier method. Median OS and TTF along with 95% confidence intervals (CIs) were reported. Associations between OS and TTF and site of metastasis were assessed using the log-rank test in univariate analysis or the Wald chi-square test from multivariable Cox regression adjusted for IMDC prognostic factors [3]. For each of these analyses, two models were undertaken. In model 1, BMs (yes vs no) and LMs (yes vs no) were evaluated as two individual factors. In model 2, patients were classified into four groups based on the combination of BMs and LMs (presence of both BMs and LMs, presence of either BMs or LMs, or other metastases). The likelihood ratio test was also conducted to test the improvement in prediction performance that was gained by the addition of BMs and LMs to the IMDC prognostic model [4].

Subgroup analyses were performed in those with (1) single and multiple sites of metastasis; (2) IMDC favorable-, intermediate-, and

Table 1 – Patient and disease characteristics at initiation of targeted therapy (*n* = 2027)

Characteristic	*n* (%)
Age at initiation of therapy	
<60 yr	945 (47)
≥60 yr	1082 (53)
Karnofsky performance score	
≥80%	1465 (72)
<80%	445 (22)
Unknown	117 (6)
Sex	
Male	1494 (74)
Female	524 (26)
Unknown	9 (<1)
Pathology	
Clear cell	1661 (82)
Non–clear cell	238 (12)
Unknown	128 (6)
Sarcomatoid features	
Yes	185 (9)
No	1599 (79)
Unknown	243 (12)
Previous nephrectomy	
Yes	1570 (78)
No	455 (22)
Unknown	2 (<1)
Previous immunotherapy	
Yes	444 (22)
No	1583 (78)
Type of targeted agent	
Sunitinib	1491 (74)
Sorafenib	357 (18)
Bevacizumab	80 (4)
Pazopanib	40 (2)
Tivozanib	7 (<1)
Axitinib	3 (<1)
Temsirolimus	42 (2)
Everolimus	7 (<1)
No. of metastases >1	1529 (75)
Metastasis site	
Lung	1390 (69)
Lymph node	864 (43)
Bone	693 (34)
Liver	381 (19)
Brain	165 (8)
Other	713 (35)
IMDC risk group	
Favorable	321 (16)
Intermediate	969 (48)
Poor	504 (25)
Unknown	233 (11)

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.