J Cancer Sci Clin Ther 2020; 4 (4): 526-537 *DOI: 10.26502/jcsct.5079092*

Research Article

The Impact of Bone Metastasis Location in the Clinical Outcome of Patients with Metastatic Renal Cell Carcinoma (mRCC): An Analysis from the Latin American Renal Cancer Group (LARCG)

Diego Abreu[1*], Antonia Angeli Gazola[2], Alessandra Borba Anton de Souza[2], Felipe Pizzolo[2], Guillermo Gueglio[3], Alberto Jurado[3], Luis Meza[4], Carlos Scorticati[5], Maximiliano Lopez[5], Stenio de Cassio Zequi[6], Walter Henriques da Costa[6], Alice Scalzilli Becker[2], Júlia Elisa Hübner[2], Rodrigo Pellegrini[2], Juan Yandian[7], Luis Ubillos[8], Noelia Ferreira[7], Marcos Tobias Machado[9], Oscar Rodriguez[10], Carlos Ameri[11], Alejandro Nolazco[12], Pablo Martinez[12], Gustavo Carvalhal[13], Pablo M. Barrios[13], Ruben Bengio[14], Leandro Arribillaga[14], Diego Muguruza[15], José Gadu[16], Edgar Bravo[16], Ricardo Castillejos[17], Francisco Rodríguez-Covarrubias[17], Pablo Mingote[18], Nicolás Ginastar[18], Rafael Alonso[19], Roberto Puente[7], Ricardo Decia[1], Gustavo Cardoso Guimarães[6], Joan Palou[10], André P. Fay[2,20]

[1]Department of Urology - Hospital Pasteur - Montevideo, Uruguay

[2] Oncology Research Group-CNPq, PUCRS, Porto Alegre, Brazil

[3]Hospital Italiano, Buenos Aires, Argentina

[4]Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru

[5]Hospital de Clinicas, Buenos Aires, Argentina

[6]A.C. Camargo Cancer Center, São Paulo, Brazil

[7]Department of Urology - Hospital de Clínicas, Montevideo, Uruguay

[8]Department of Medical Oncology - Hospital de Clinicas, Montevideo, Uruguay

[9]Escuela de Medicina ABC, San Pablo, Brazil

[10]Fundación Puigvert, Barcelona, Spain

[11]Hospital Alemán, Buenos Aires, Argentina

[12]Hospital Británico, Buenos Aires, Argentina

[13]PUCRS School of Medicine, Porto Alegre, Brazil

[14]Clinica Profesor Bengio, Cordoba, Argentina

[15]COMEPA, Paysandu, Uruguay

[16]Hospital Militar, Ciudad de México, México

[17]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCNSZ), Ciudad de México, México

[18]Policlinico Neuquén, Neuquén, Argentina

[19]Department Quantitative Methods, Faculty of Medicine, Montevideo, Uruguay

[20]Department of Medical Oncology - Hospital Sao Lucas da PUCRS, Porto Alegre, Brazil

***Corresponding Author:** Dr. Diego Abreu, Department of Urology - Hospital Pasteur - Montevideo, Uruguay, Mobile Phone: 00598 99697153; E-mail: die.abreu@gmail.com

Received: 29 September 2020; **Accepted:** 12 October 2020; **Published**: 27 October 2020

Citation: Diego Abreu, Antonia Angeli Gazola, Alessandra Borba Anton de Souza, Felipe Pizzolo, Guillermo Gueglio, Alberto Jurado, Luis Meza, Carlos Scorticati, Maximiliano Lopez, Stenio de Cassio Zequi, Walter Henriques da Costa, Alice Scalzilli Becker, Júlia Elisa Hübner, Rodrigo Pellegrini, Juan Yandian, Luis Ubillos, Noelia Ferreira, Marcos Tobias Machado, Oscar Rodriguez, Carlos Ameri, Alejandro Nolazco, Pablo Martinez, Gustavo Carvalhal, Pablo M. Barrios, Ruben Bengio, Leandro Arribillaga, Diego Muguruza, José Gadu, Edgar Bravo, Ricardo Castillejos, Francisco Rodríguez-Covarrubias, Pablo Mingote, Nicolás Ginastar, Rafael Alonso, Roberto Puente, Ricardo Decia, Gustavo Cardoso Guimarães, Joan Palou, André P. Fay. The Impact of Bone Metastasis Location in the Clinical Outcome of Patients with Metastatic Renal Cell Carcinoma (mRCC): An Analysis from the Latin American Renal Cancer Group (LARCG). Journal of Cancer Science and Clinical Therapeutics 4 (2020): 526-537.

Abstract

Background: Tumor burden and metastatic disease sites are well-established prognostic factors in many malignancies, including metastatic Renal Cell Carcinoma (mRCC).

Objective: We aimed to evaluate the impact of bone metastasis (BM) location on clinical outcome of mRCC patients.

Methods: This study is a retrospective analysis of 4060 mRCC patients from the Latin American Renal Cancer Group (LARCG) database. Clinico-pathological characteristics, 24-months-survival, overall survival (OS), and BM sites were collected. To estimate the association between BM location and clinical outcomes we used Cox regression method.

Results: Out of 4060 patients, 530 (14.5%) had metastatic disease. Among those, we analyzed the fifty-six that had only BM. The median follow-up was 20.8 months (range from 0 to 188 months). Non-spinal BM (NSBM) were identified in 33 (58.9%) patients and spinal BM (SBM) in 23 (41.1%) patients. Median OS was 35 months, and 24-months OS was 76% for patients with NSBM and 46% with SBM (HR: 2.22). In multivariable analysis SBM (HR: 3.08), ASA classification 3-4 (HR: 2.37), non-cc histology (HR: 5.11), and age (HR 1.06) were independent prognostic factors for OS.

Conclusions: Our study showed that SBM predicted shorter OS, suggesting that the location of BM may impact the clinical outcome of patients with mRCC.

Keywords: Renal Cell Carcinoma; Spine metastasis; Vertebral metastasis; Kidney Cancer; Metastasis site

Abbreviations: mRCC- Metastatic Renal Cell Carcinoma; RCC- Renal Cell Carcinoma; BM- Bone Metastasis; SBM- Spinal Bone Metastasis; NSBM- Non-spinal Bone Metastasis; SRE- Skeletal Related Events; OS- Overall Survival; IMDC- International Metastatic Renal Cell Carcinoma; MSKCC- Memorial Sloan-Kettering Cancer Center (MSKCC/Motzer) Score; LARCG- Latin American Renal Cell Group; VEGF- Vascular Endothelial Growth Factor; BMI- Body Mass Index; ECOG- Eastern Cooperative Oncology Group; ASA-American Society of Anesthesiologists; cc- Clear Cell; non-cc- non-Clear Cell; mTOR- mammalian target of rapamycin; KPS- Karnofsky Performance; LDH- High Lactate Dehydrogenase; CSS- Cancer-specific Survival

1. Introduction

Of all renal cancers, RCC is the most common subtype, corresponding to 85% of all RCC cases, and being responsible for 15,000 of Americans diagnosed annually according to the American Cancer Society [1, 2]. Approximately 30% of patients treated with a curative-intent surgical resection of a localized renal tumor will develop metastatic disease [3]. Tumor burden and metastatic disease sites are well-established prognostic factors in many malignancies, including metastatic renal cell carcinoma (mRCC).

Approximately 30% of patients with mRCC have bone metastasis (BM) which is associated with significant morbidity and high rates of skeletal complications, resulting in a shorter overall survival [4]. There is increasing evidence that the presence of BM harms mRCC prognosis, being a predictor of poor progression-free survival (PFS) and overall survival (OS) among this population [5]. It is estimated that nearly 70% of patients with mRCC will develop at least one skeletal-related event (SRE) during the disease course when BM is present [6]. Close to 5% of patients with BM have exclusively BM at diagnosis and spinal metastasis is associated with poor prognosis [7, 8]. A recent systematic review published by Goodwin et al. including 807 patients showed that from the time of spinal metastasis diagnosis the median survival was 11,7 months [9].

The identification of prognostic factors is important to tailor treatment options, to stratify risks, and to offer counseling for mRCC patients [10]. International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and MSKCC prognostic risk scores are widely used to define treatment strategies in mRCC [1]. In this analysis, we sought to evaluate the impact of BM location in the clinical outcome of mRCC patients in a large multicentric cohort from a Latin American population.

2. Methods

The Latin American Renal Cancer Group (LARCG) is a multi-institutional and multidisciplinary group that established a database on Renal Cancer [11]. LARCG involves 45 centers from 8 countries including Uruguay, Brazil, Argentina, Mexico, Peru, Chile, Bolivia, and Spain. Data was collected using medical records, and pathological reports from each institution with a total of 4,060 renal cancer cases.. The primary objective of this analysis was to evaluate the impact of BM location in the prognosis of mRCC patients who have exclusively bone metastasis. Clinico-pathological characteristics such as age, sex, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) Performance Status, American Society of Anesthesiologists (ASA) and Karnowski performance

status, symptoms at presentation, tumor size, lymph node staging, nuclear Fuhrman grade, perirenal fat invasion, necrosis, histological subtype, sarcomatoid differentiation of the BM, the realization of cytoreductive nephrectomy, the primary form of treatment of the metastasis, administration of systemic therapy, survival status and location of BM were collected using standard templates.

Chi-square and Fisher's exact tests were used to evaluate the relationships between clinical and pathologic variables between spinal and non-spinal. The significance level of the tests was fixed at 0.05. Kaplan-Meier product-limit method was used to estimate OS and CSS at 60 months, and differences in the curves were assessed using log-rank tests (Figure 1). Survival time was calculated as the difference between the date of surgery and the date of last follow-up or death. Univariate and multivariate Cox proportional hazards regression models were used to evaluate the relationship between clinical and pathologic variables with OS and CSS. For the Cox model, variables with less than 15% of missing values were considered. After that, multiple imputations were used to replace missing values. The mi and ice library of Stata software was used for the multiple imputations.

Variables associated with survival in univariate analysis with ($p<0.2$) were included for multivariate modeling. The proportional risk assumption was evaluated graphically and using Schoenfeld residuals. The Statistical Package for Social Sciences software v. 24 (SPSS) and Stata software were used for the calculation.

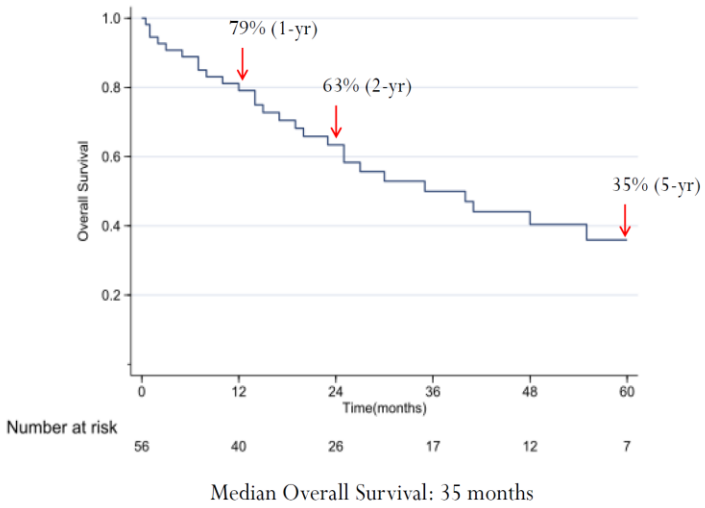

Figure 1: Overall Survival for the entire patient cohort.

3. Results

We identified 530 (14.5%) patients with metastatic disease out of 4060 from the LARCG dataset. From 530, 56 (10.5%) had exclusively BM. The median follow-up was 20.8 months (0-188 range). Our population was mostly under 65 years (66.1%), and male (64.3%), where the median age was 59.5 (40-85), and the number of male participants was 36 (64.3%). Most patients presented symptoms at diagnosis (90.6%). We examined histological subtypes and found that 42 (85.7%) patients had clear cell

histology, and 7 (14.3%) patients had non-clear cell histology (1 (2%) had papillary histology, 2 (4.1%) had chromophobe histology, 1 (2%) had unclassified histology, and 3 (6.1%) had other histological subtypes). Sarcomatoid differentiation was identified in 8 (19%) patients. Cytoreductive nephrectomy was performed in 46 patients (82.1%). 35 (68.6%) patients received anti-VEGF/ mTOR systemic therapy for kidney cancer, 1 (2%) received cytokines (interferon and interleukin-2) and 15 (29.4%) had no systemic therapy (Table 1 and 2).

	Bone Metastasis (BM)			
Variable	**All Cases (n=56)**	**Non-Spinal (n=33)**	**Spinal (n=23)**	***P***
Age (years)				
Median	59.5	60	58	0.585
Range	(40-85)	(40-84)	(43-85)	
Age				
< 65	37 (66.1)	22 (66.7)	15 (65.2)	0.910
≥ 65	19 (33.9)	11 (33.3)	8 (34.8)	
Gender				
Male	36 (64.3)	17 (51.5)	19 (82.6)	0.017
Female	20 (35.7)	16 (48.5)	4 (17.4)	
BMI				
< 25	14 (35)	8 (36.4)	6 (33.3)	0.842
≥ 25	26 (65)	14 (63,6)	12 (66.7)	
ECOG PS				
0	11 (20)	7 (21,2)	4 (18.2)	0.904
1	33 (60)	20 (60.6)	13 (59.1)	
≥ 2	11 (20)	6 (18.2)	5 (22.7)	
ASA				
1-2	33 (61.1)	21 (65,6)	12 (54.5)	0.412
3-4	48 (90.6)	11 (34,4)	10 (45.5)	
Symptoms at Presentation				
No	5 (9.4)	3 (9.4)	2 (9.5)	0.986
Yes	48 (90.6)	29 (90.6)	19 (90.5)	
Size (pT)				
≤ 7 cm	27 (58.7)	16 (59.3)	11 (57.9)	0.926
> 7 cm	19 (41.3)	11 (40.7)	8 (42.1)	

Table 1: Sociodemographic and Clinical characterization of this Study´s Patients-Part I.

This table represents the sociodemographic and clinical characterization of the study, differentiating our patients between SBM or NSBM. Our population was primarily under 65 years of age and male, and there was significant (p=0.017) correlation between sex and spinal metastasis.

	Bone Metastasis (BM)			
Variable	**All Cases (n=56)**	**Non-Spinal (n=33)**	**Spinal (n=23)**	***P***
Stage (pN)				
pN0	25 (86.2)	15 (88.2	10 (83.3)	0.706
pN1	4 (13.8)	2 (11.8)	2 (16.7)	
Fuhrman				
1-2	13 (29.5)	8 (32)	5 (26.3)	0.682
3-4	31 (70.5)	17 (68)	14 (73.7)	
Perirenal Fat Invasion				
No	26 (63.4)	15 (62.5	11 (64.7)	0.885
Yes	15 (36.6)	9 (37.5)	6 (35.3)	
Necrosis				
No	17 (42.5)	8 (34.8)	9 (52.9)	0.251
Yes	23 (57.5)	15 (65.2)	8 (47.1)	
Subtype istological				
Clear cell	42 (85.7)	25 (89.3)	17 (81)	0.572
Papillary	1 (2)	1 (3.6)	0 (0)	
Chromophobe	2 (4.1)	1 (3.6)	1 (4.8)	
Unclassified	1 (2)	0 (0)	1 (4.8)	
Others	3 (6.1)	1 (3.6)	2 (9.5)	
Sarcomatoid differentiation				
No	34 (81)	22 (91.7)	12 (66.7)	0.041
Yes	8 (19)	2 (8.3)	6 (33.3)	
Citoreductive Nephrectomy				
No	10 (17.9)	5 (15.2)	5 (21.7)	0.822
Yes	46 (82.1)	28 (84.8)	18 (78.3)	
Treatment of Metastasis				
Surgery	7 (35)	4 (36.3)	3 (33.3)	
Radiotherapy	8 (40)	4 (36.3)	4 (44.4)	
Others	5 (25)	3 (27.3)	2 (22.2)	

Systemic Therapy				
Anti-VEGF/mTOR	35 (68.6)	20 (66.7)	14 (70)	
Cytokines IFN/IL2	1 (2)	1 (3.3)	0 (0)	
No ST	15 (29.4)	9 (30)	6 (30)	
Status Survival				
Alive	24 (43.6)	16 (50)	8 (34.8)	
Dead	31 (56.4)	16 (50)	15 (65.2)	
Dead by Cancer	29 (93.6)	15 (93.8)	14 (93.3)	

Table 2: Sociodemographic and Clinical characterization of this Study´s Patients-Part II.

This table represents the sociodemographic and clinical characterization of the study, differentiating our patients between SBM or NSBM. Most of our patients presented with clear cell carcinoma and had received cytoreductive nephrectomy as the primary surgical approach and anti-VEGF/mTor as principal systemic therapy. There was a significant (p=0.041) correlation between having sarcomatoid differentiation of the tumor and spinal metastasis. Among the 56 patients with exclusively BM, 33 (58.9%) had NSBM and 23 (41.1%) had SBM. 18 patients (32.1%) presented with a single BM, while 38 (67.9%) had multiple metastases (Table 3).

	Bone Metastasis (BM)		
Location	**All Cases (n=56)**	**Single (n=18)**	**Multiple (n=38)**
Upper Limbs	5 (8.9)	3 (60)	2 (40%)
Lower Limbs	8 (14.3)	5 (62.5)	3 (37.5)
Pelvic	5 (8.9)	3 (60)	2 (40)
Spine	13 (23.2)	5 (38.5)	8 (61.5)
Thorax	4 (7.1)	1 (25)	3 (75)
Skull	2 (3.6)	1 (50)	1 (50)
Limbs (both)	1 (1.8)	0 (0)	1 (100)
Spine + Limbs	3 (5.4)	0 (0)	3 (100)
Spine + Pelvic	3 (5.4)	0 (0)	3 (100)
Spine + Thorax	4 (7.1)	0 (0)	4 (100)
Pelvic + Limbs	3 (5.4)	0 (0)	3 (100)
Thorax + Limbs	5 (8.9)	0 (0)	5 (100)

Table 3: Bone Metastasis Locations among all Analysed Patients.

We separated our patients per location and number of metastasis. Most of our population did not have spinal metastasis (n=33) and had multiple bone metastases (n=38). Factors positively associated with SBM were Sarcomatoid differentiation (p=0.041) and male gender (p=0.017). The 24-month OS for the entire patient cohort was 63%, and the median OS was 35 months (Figure 1). Univariable analysis showed associations between OS and the presence ASA classification 3-4 (HR 2.38, 95% CI 1.04 - 5.43, p<0.04) and SBM (HR 2.22, 95% CI 1.03 - 4.77, p=0.041). The 24-month OS for patients with NSBM was 76% and, for patients with SBM, 46%, and median OS for NSBM and SBM was 55 and 19 months, respectively (Figure 2).

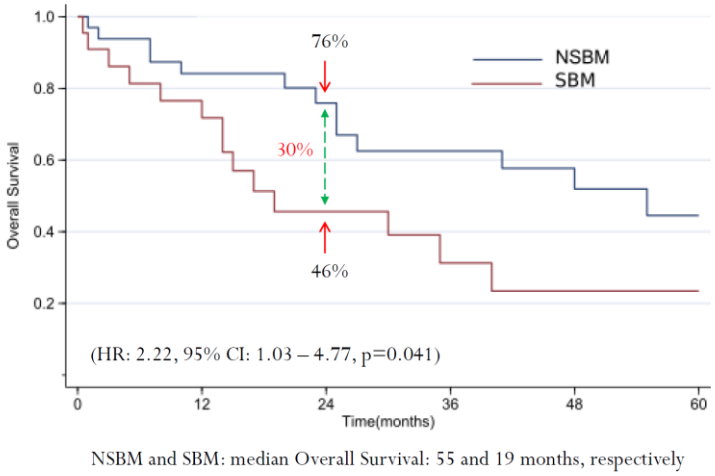

Figure 2: Overall Survival: a Comparison Between Groups with Spinal Bone Metastasis and Non-spinal Bone Metastasis.

In multivariate analysis were independent prognostic factors of 5-year OS, SBM (HR 3.08, 95% CI 1.31-7.23, p=0.010), ASA 3-4 (HR 2.37, 95% CI 1.00 -5.61, p=0.05), non-cc histology (HR 5.11, 95% CI 1.66 -15.71, p<0.004) and AGE (HR 1.06, 95% CI 1.01-1.11, p=0.012) (Table 4).

5-year Overall Survival							
Variable	**Univariable**			**Multivariable**			
	HR	[95% CI]	P	HR	[95% CI]		P
BM (SBM vs NSBM)	2.22	1.03-4.77	0.041	3.08	1.31	7.23	0.01
AGE	1.04	1.00-1.08	0.071	1.06	1.01	1.11	0.012
ASA (3-4 vs 1-2)	2.38	1.04-5.43	0.040	2.37	1.00	5.61	0.05
Histology (non-cc vs cc)	2.19	0.84-5.75	0.110	5.11	1.66	15.71	0.004
Metastases (multiple vs single)	1.96	0.79-4.86	0.148	-	-	-	-
Gender (male vs female)	1.29	1.06-2.80	0.513	-	-	-	-
ECOG (≥ 1 vs 0)	1.68	0.58-4.85	0.339	-	-	-	-

Table 4: Cox regression analysis for overall survival (OS).

In the left, we separated the variables, distinguishing between univariable and multivariable analysis. We reported the Hazard Ratio (HR), Confidence Interval (CI) and statistical significance (p) of each variable.

4. Discussion

Data concerning the natural history and treatment-related outcomes amongst mRCC patinets in Latin America are lacking. Bone metastasis has been associated with poor clinical outcome in patients with mRCC. In our series of 530 mRCC patients, 10.5% had exclusively bone metastasis, comparable to the study by Bianchi et al (12%), from an extensive database of 11.157 cases of mRCC [12]. Another study, performed by Woodward et al structured a cohort of RCC patients and analyzed the development of bone metastases. Patient demographics were mostly of fair-skinned man (71% male). Their cohort also detected the predominance of clear cell histology (83%), corroborating our data (85.7%) [4].

The median OS in our cohort was 35 months, and survival rates at 1 and 5 years were 79% and 35%, respectively. Similar results were reported by Szendrői et al (1 and 5 years OS, 75%, and 35%, respectively [13], Althausen (84% and 55%, respectively), and Tobisu et al (77% and 45%, respectively) [14, 15]. Survival outcomes in mRCC significantly increased from approximately 9 months in the immunotherapy era (2002-2005) to 30 months in the target therapies era [16]. However, in our cohort, the high survival rate may have been influenced by the number of patients who underwent cytoreductive nephrectomy (82%) and systemic treatment (68.6%). Against this, a small number of patients (12.5%) underwent surgery for metastasis, and isolated metastasectomy or associated systemic treatment has shown a longer OS [13, 17].

Other findings from our cohort were the high percentage of cases with Fuhrman grade 3-4 (70%), and the presence of sarcomatoid differentiation in 19% (8/56) of the cases. Regarding this last characteristic, our analysis could indicate that spinal metastasis is more likely to happen in RCC with sarcomatoid differentiation. Nevertheless, our study did not find a statistically significant association in the univariate analysis, which was reported in previous studies, being able to influence the high number of lost data [14, 18]. YueJun et al described similar results to ours in the Fuhrman grade 3-4 percentage (78.2%), with an increased sarcomatoid differentiation in their cohort (84.2%), which could be the cause of the lower median OS (7.6%) in the non-metastasectomies patients' group [18].

The location of BM and its impact on the clinical outcome were the main purposes of our analysis. Many studies have sought this analysis, comparing mainly the appendicular versus axial topography. The results have been contradictory, once appendicular BM had a better prognosis [14, 19] and others could not demonstrate the same [20, 21]. We found that the prognosis is worse when the BM topography is of spinal location, compared to the non-spinal. Patients with SBM had 24 months OS 30% lower than the ones with NSBM. In multivariate analyses, SBM, ASA 3-4, non-cc histology, and age were an independent prognostic factor of 5-year OS. Having SBM implies a 3-fold increase in the risk of death in our multivariate model, which is consistent with previous literature results.

Kume et al reported SBM as an independent prognostic value for poor OS. Also, sarcomatoid differentiation, extraosseous metastasis, alkaline phosphatase increased to 1.5 times the upper limit of normal, and C-reactive protein increased to greater than 0.3 mg/dl were shown to be significant risk factors [8]. Our group previously reported

that ASA 3-4 is a prognostic variable for OS, both in mRCC and in localized RCC [22, 23]. This classification can be a very useful tool, considering it is simple and reproducible.

When it comes to assessing prognosis for mRCC, two systems commonly used are the MSKCC model and the IMDC model. The MSKCC model was developed in the era of immunotherapy, and its adverse prognostic factors are low Karnofsky performance status (KPS), high lactate dehydrogenase (LDH), low serum hemoglobin, high corrected serum calcium, and interval from diagnosis to treatment of less than 1 year [24]. With the advent of targeted therapy, it became necessary to validate the prognosis criteria in the setting of these new treatments, and the IMDC model was developed. This system adds neutrophil and platelet count to four factors already used in the MSKCC model [25]. Recently, a study was published by Massari et al. which aim was to evaluate if the addition of a new independent variable could improve IMDC prognosis prediction and reduce heterogeneity within the risk category [26]. Besides other variables included in the IMDC score, the presence of brain, bone, and/or liver as the first site of metastatic disease was significantly associated with OS, since 15% of patients modified their initial risk category [26]. This seems to be a good example to follow, analyzing and including variables, such as the topography of BM, may allow us to use more accurate prognostic models that help make a better therapeutic decision.

We reported for the first time the role of prognostic factors in a small international cohort of BM in Latin America. The main limitations of this study are inherent to its retrospective nature and the absence of IMDC or MSKCC prognostic scores for all patients. Additionally, the absence of a central pathology review limits our assessment of certain elements such as sarcomatoid histology and other non-clear cell subtypes. Treatment discrepancies among different centers may have led to variations in clinical presentation, surgical technique, and patient adherence to follow-up.

5. Conclusions

Our study showed that SBM predicted shorter OS, suggesting that the location of BM may impact the clinical outcome of patients with mRCC. ASA 3-4, non-cc histology, and age were an independent prognostic factor of OS. External validation of this data could lead to a simple and straightforward prognostic tool for patients with BM of renal cell carcinoma.

Acknowledgements

The authors recognize the participation of the following LARCG members in providing data or input for the study: Patricio Garcia, Ana Maria Autran, Lucas Nogueira, Fernando Secin, Jose Vazquez, Deusdedit Vieira Cortez da Silva Neto, Daniel Beltrame Ferreira, Agustin Rovegno, Raul Langenhin, Jorge Clavijo, Omar Clark, Miguel Sánchez, Carmen González Antonio Carlos Lima Pompeo, Martin Varela, Pablo Bouza, Ana Vilas and Alvaro Zuñiga.

Conflicts of Interest

The authors have no disclosures or conflicts of interest regarding this research and manuscript.

References

1. Langdon J, Way A, Heaton S, et al. The management of spinal metastases from renal cell carcinoma. Ann R Coll Surg Engl 91 (2009): 649-652.
2. David A. Swanson, William L. Orovan, Douglas E. Johnson, et al. Osseous metastases secondary to renal cell carcinoma. Urology 18 (1981): 556-561.

3. Taunk NK, Spratt DE, Bilsky M, et al. Spine radiosurgery in the management of renal cell carcinoma metastases. JNCCN J Natl Compr Cancer Netw 13 (2015): 801-809.
4. Woodward E, Jagdev S, McParland L, et al. Skeletal complications and survival in renal cancer patients with bone metastases. Bone 48 (2011): 160-166.
5. Beuselinck B, Oudard S, Rixe O, et al. Negative impact of bone metastasis on outcome in clear-cell renal cell carcinoma treated with sunitinib. Ann Oncol 22 (2011): 794-800.
6. 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 8 (2013): 6-12.
7. Santoni M, Conti A, Procopio G, et al. Bone metastases in patients with metastatic renal cell carcinoma: Are they always associated with poor prognosis? J Exp Clin Cancer Res 34 (2015): 1-9.
8. Kume H, Kakutani S, Yamada Y, et al. Prognostic factors for renal cell carcinoma with bone metastasis: Who are the long-term survivors? J Urol 185 (2011): 1611-1614.
9. Goodwin CR, Ahmed AK, Boone C, et al. The Challenges of Renal Cell Carcinoma Metastatic to the Spine: A Systematic Review of Survival and Treatment. Glob Spine J 8 (2018): 517-526.
10. Li H, Samawi H, Heng DYC. The use of prognostic factors in metastatic renal cell carcinoma. Urol Oncol Semin Orig Investig 33 (2015): 509-516.
11. Zequi S de C, Abreu D, Nolazco A, et al. The creation, development and diffusion of the larcglatin american renal cancer group. Int Braz J Urol 43 (2017): 3-6.
12. Bianchi M, Sun M, Jeldres C, et al. Distribution of metastatic sites in renal cell carcinoma: A population-based analysis. Ann Oncol 23 (2012): 973-980.
13. Szendrői A, Dinya E, Kardos M, et al. Prognostic factors and survival of renal clear cell carcinoma patients with bone metastases. Pathol Oncol Res 16 (2010): 29-38.
14. Althausen P, Althausen A, Jennings LC, et al. Prognostic factors and surgical treatment of osseous metastases secondary to renal cell carcinoma. Cancer 80 (1997): 1103-1109.
15. Tobisu K, Kakizoe T, Takai K TY. Prognosis in renal cell carcinoma: analysis of clinical course following nephrectomy. Jpn J Clin Oncol 19 (1989): 142-148.
16. Judith Manola, Patrick Royston, Paul Elson, et al. Prognostic Model for Survival in Patients with Metastatic Renal Cell Carcinoma: Results from the International Kidney Cancer Working Group. Clin Cancer Res 17 (2011): 5443-5450.
17. Vallet S, Pahernik S, Höfner T, et al. Efficacy of targeted treatment beyond third-line therapy in metastatic kidney cancer: Retrospective analysis from a large-volume cancer center. Clin Genitourin Cancer 13 (2015): e145-e152.
18. Du YJ, Pahernik S, Hadaschik B, et al. Survival and prognostic factors of patients with renal cell cancer with bone metastasis in the era of targeted therapy: A single-institution analysis. Urol Oncol Semin Orig Investig 34 (2016): 433.e1-433.e8.
19. Jung ST, Ghert MA, Harrelson JM SS. Treatment of osseous metastases in patients with renal cell carcinoma. Clin Orthop Relat Res (2003): 223-231.
20. Han KR, Pantuck AJ, Bui MHT, et al. Number of metastatic sites rather than location dictates overall survival of patients with node-negative metastatic renal cell carcinoma. Urology 61 (2003): 314-319.

21. Fottner A, Szalantzy M, Wirthmann L, et al. Fottner, Andreas Szalant (2010): 2-7.
22. Mourão TC, Abreu D, Carvalhal GF, et al. Small renal masses in Latin-American population: characteristics and prognostic factors for survival, recurrence and metastasis - a multi-institutional study from LARCG database. BMC Urol 20 (2020): 85.
23. de Cássio Zequi S, de Campos ECR, Guimarães GC, et al. The Use of the American Society of Anesthesiology Classification as a Prognostic Factor in Patients with Renal Cell Carcinoma. Urol Int (2010): 67-72.
24. Motzer BRJ, Bacik J, Murphy BA, et al. Interferon-Alfa as a Comparative Treatment for Clinical 20 (2002): 289-296.
25. Heng DYC, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. J Clin Oncol 27 (2009): 5794-5799.
26. Massari F, Di Nunno V, Guida A, et al. Addition of Primary Metastatic Site on Bone, Brain, and Liver to IMDC Criteria in Patients With Metastatic Renal Cell Carcinoma: A Validation Study. Clin Genitourin Cancer (2020): 1-9.