Prognostic Factors in De Novo Metastatic Renal Cell Carcinoma: A Report From the Latin American Renal Cancer Group

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abstract

PURPOSE To assess the effect of clinical and pathological variables on cancer-specific and overall survival (OS) in de novo metastatic patients from a collaborative of primarily Latin American countries.

PATIENTS AND METHODS Of 4,060 patients with renal cell carcinoma diagnosed between 1990 and 2015, a total of 530 (14.5%) had metastasis at clinical presentation. Relationships between clinical and pathological parameters and treatment-related outcomes were analyzed by Cox regression and the log-rank method.

RESULTS Of 530 patients, 184 (90.6%) had died of renal cell carcinoma. The median OS of the entire cohort was 24 months. American Society of Anesthesiology classification 3-4 (hazard ratio [HR]: 1.64), perirenal fat invasion (HR: 2.02), and ≥ 2 metastatic organ sites (HR: 2.19) were independent prognostic factors for 5-year OS in multivariable analyses. We created a risk group stratification with these variables: no adverse risk factors (favorable group), median OS not reached; one adverse factor (intermediate group), median OS 33 months (HR: 2.04); and two or three adverse factors (poor risk group), median OS 14 months (HR: 3.58).

CONCLUSION Our study defines novel prognostic factors that are relevant to a Latin American cohort. With external validation, these easily discerned clinical variables can be used to offer prognostic information across low- and middle-income countries.

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INTRODUCTION

Renal cell carcinoma (RCC) represents a tumor type with highly variable outcomes and accounts for 2%-3% of all cancers. It is estimated that 338,000 new RCC cases occur each year worldwide, and its highest incidence has been observed in North America and Eastern and Northern Europe. Mortality rates because of RCC have stabilized in most developed countries but are increasing in Latin America.1,2 Mortality rates are still high because 20%-30% of patients with RCC have metastatic disease at presentation, with a further 20%-30% progressing to metastatic disease after initial treatment.1,2 In the latter group, more than 90% of metachronous metastases present within 5 years.3 Most data concerning the epidemiology of metastatic RCC (mRCC) are derived from studies performed in Europe and North America.1,4 There is lack of data on the clinical and pathologic characteristics of mRCC within Latin America. Given this void, the Latin American Renal Cancer Group has undertaken a collaborative study involving centers of excellence for patients with RCC within Latin America and Spain. The aim of this study was to identify prognostic factors for cancer-specific survival (CSS) and overall survival (OS) in patients presenting with de novo mRCC and to derive clinical prognostic variables for use in counseling patients.

PATIENTS AND METHODS

Patient Population

Of the 4,060 patients with RCC who were treated at 28 institutions from eight Latin American countries (Uruguay, Brazil, Argentina, Mexico, Chile, Peru, Bolivia, and Spain), 530 patients presented with metastasis and were included in the study. All the enrolled subjects provided written informed consent, and Protocols were approved by the local Ethical Committees.
The clinical variables obtained for analysis were age, sex, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG-PS), American Society of Anesthesiology (ASA) risk classification, the presence of symptoms at diagnosis, and serum hemoglobin levels. Clinical staging was coded according to the 2010 American Joint Committee on Cancer (TNM) staging. Pathologic variables included histologic subtype according to the 2004 WHO, tumor size, nodal status, Fuhrman, necrosis, perirenal fat invasion, vein invasion, and sarcomatoid features. Staging included computed tomography or magnetic resonance imaging of the abdomen and pelvis, and a chest x-ray. Bone scans were performed selectively.

Statistical Analysis
Survival time was calculated as the difference between the date of diagnosis and the date of last follow-up or death. Chi-square and Fisher’s exact tests were used to comparing qualitative variables. The Kaplan-Meier product limit method was used to estimate OS and CSS, and differences in the curves were assessed using log-rank tests. Univariate and multivariate Cox proportional hazards regression models were used to evaluate the relationship of clinical and pathologic variables with OS and CSS. Only significantly associated variables with survival in univariate analysis (P < .1) were included for multivariate modeling. The proportional hazards assumption was evaluated using Schoenfeld residuals. We created a risk group stratification according to the variables that were significantly associated with OS in the multivariable analysis. The model of risk group stratification was compared with the multivariable model using the Bayesian information criterion. The Statistical Package for Social Sciences software (v. 19) and Stata v16 were used.

RESULTS
Patient Characteristics and Outcomes
The median age of the 530 patients was 61 years (23-94 years): 359 (68%) patients were male and 169 (32%) were female. The median follow-up was 6 months (0-162 months) and 13 months excluding those patients alive with < 6 months of follow-up. Of the 530 patients, 203 died (38.3%), of which 184 (90.6%) died of RCC. Of 451 patients with data on the number of metastases, 111 (24.6%) and 340 (75.4%) had single and multiple metastases, respectively. The organs most frequently affected with metastasis were lungs (45.5%), bone (21.5%), lymph nodes (10.6%), liver (8.7%), adrenals (4%), and brain (2.2%). Among patients with multiple metastases, a single organ was affected in 173 cases (51%), two organs in 128 cases (37.8%), three organs in 36 cases (10.6%), and four organs in two cases (0.6%). In 511 of the 530 patients (96.4%), nephrectomies were performed, 483 of which were radical (94.5%) and 28 partial (5.5%). Further treatment for metastases was performed in 177 patients (34.1%), of whom 124 (70%) received systemic treatments: 95 (76.6%) received tyrosine kinase inhibitors and 29 (23.4%) were treated with immunotherapy (either interferon-alpha or interleukin-2). Sixteen patients received radiotherapy to metastatic sites (9%), 5 patients (2.8%) underwent metastasectomies, whereas 31 patients (17.5%) received other treatments (Table 1).

Univariate and Multivariate Analysis
Factors positively associated with multiple metastases were positive lymph nodes (pN1) (P = .010), Fuhrman ≥ 3 (P = .008), perirenal fat invasion (P = .019), necrosis (P < .0001), nonclear cell histology (P = .042), and serum Hb < 11 g/dL (P = .007). Metastases in ≥ 2 organ sites were associated with ECOG-PS ≥ 1 (P = .004), pN1 (P = .001), renal vein invasion (P = .042), and nonclear cell subtype (P = .003). Interestingly, BMI ≥ 25 kg/m² was associated with the presence of a single-organ site and single metastasis (P = .018) (Tables 2 and 3).

The median OS for the whole cohort was 24 months (95% CI, 18.1 to 29.8), and the 2-year OS was 48% (Fig 1). Excluding patients with < 6 months of follow-up, the median follow-up was 13 months and median OS was 22 months, with a 2-year OS of 46%.
Univariate analysis showed associations between 5-year OS and CSS and the presence of ECOG-PS ≥ 1 (P = .005 and P = .007), ASA classification 3-4 (P = .0001 for both), pT3-4 (P = .019 and P = .009), pN1 (P = .001 and P = .0001), Fuhrman ≥ 3 (P = .010 and P = .008), necrosis (P = .024 and P = .016), perirenal fat invasion (P = .0001 for both), Hb, 11 g/dL (P = .001 and P = .002), multiple metastases (P = .002 and P = .001), and ≥ 2 involved organs (P = .002 and P = .005).

The median OS and CSS were both 43 months in the presence of a single metastasis and 16 months and 20 months, respectively, for multiple metastases. Two-year OS and CSS were 67% and 70% for single metastasis, and 44% and 45% for multiple metastases, respectively (hazard ratio [HR] for OS: 1.94, 95% CI, 1.28 to 2.95, P = .002 and HR for CSS: 2.07, 95% CI, 1.33 to 3.23, P = .001) (Fig 2).

The median OS and CSS were both 30 months and 33 months, respectively, for patients with metastasis in a single organ and were both 14 months for patients with ≥ 2 involved organs. Two-year OS and CSS were 55% and 56% for patients with metastasis in a single organ and 36% and 38% for patients with metastases in multiple organs, respectively (HR for OS: 1.67, 95% CI, 1.21 to 2.32, P = .002).

**TABLE 1. Patients’ Clinical and Pathologic Characteristics**

| Variable                        | Total No. Patients Evaluated (N = 530) | Patients No. % |
|--------------------------------|----------------------------------------|----------------|
| Age, years                     |                                        |                |
| Median                         |                                        | 491 61         |
| Range                          |                                        | 23-94          |
| Sex                            |                                        |                |
| Male                           |                                        | 528 359 68     |
| Female                         |                                        | 169 32         |
| ECOG PS                        |                                        | 373 76 20.4    |
| 0                              |                                        | 297 79.6       |
| ≥ 1                            |                                        |                |
| ASA                            |                                        | 342 232 67.8   |
| 1-2                            |                                        | 110 32.2       |
| 3-4                            |                                        |                |
| Symptoms at presentation       |                                        | 489 114 23.3   |
| No                             |                                        | 375 76.7       |
| Yes                            |                                        |                |
| Histologic subtype             |                                        | 347 285 82.1   |
| Clear cell                     |                                        | 9 2.6          |
| Papillary                      |                                        | 4 1.2          |
| Chromophobe                    |                                        | 15 4.3         |
| Unclassified                   |                                        | 34 9.8         |
| Sarcomatoid differentiation    |                                        |                |
| Nephrectomy                    |                                        | 511 483 94.5   |
| Radical                        |                                        | 28 5.5         |
| Partial                        |                                        |                |
| Treatment of metastasis        |                                        | 177 5 2.8      |
| Surgery                        |                                        | 16 9.0         |
| Radiotherapy                   |                                        | 31 17.5        |
| Other                          |                                        |                |
| Immunotherapy                  |                                        | 177 17 9.6     |
| IFN                            |                                        | 8 4.5          |
| IFN + IL-2                     |                                        | 1 0.6          |
| Second-line anti-VEGF after    |                                        | 177 3 1.7      |
| Immunotherapy                  |                                        | 2 1.1          |
| Anti-VEGF                      |                                        |                |
| Systemic therapy               |                                        | 177 63 35.6    |
| Sunitinib                      |                                        | 12 6.8         |
| Pazopanib                      |                                        | 6 3.4          |
| Sorafenib                      |                                        | 5 2.8          |
| Bevacizumab                    |                                        | 2 1.1          |
| Temsirolimus                   |                                        | 5 2.8          |
| Anti-VEGF + others             |                                        |                |

*Table continued in next column*

**TABLE 1. Patients’ Clinical and Pathologic Characteristics (Continued)**

| Variable                        | Total No. Patients Evaluated (N = 530) | Patients No. % |
|--------------------------------|----------------------------------------|----------------|
| Metastases                     |                                        | 451 111 24.6   |
| Single                         |                                        | 340 75.4       |
| Multiple                       |                                        |                |
| Metastases                     |                                        | 339 173 51     |
| 1 organ                        |                                        | 166 49         |
| ≥ 2 organs                     |                                        |                |
| Metastatic site                |                                        | 321 146 45.5   |
| Lungs                          |                                        | 69 21.5        |
| Bone                           |                                        | 28 8.7         |
| Liver                          |                                        | 7 2.2          |
| Brain                          |                                        | 13 4           |
| Adrenal gland                  |                                        | 34 10.6        |
| Lymph node                     |                                        | 24 7.5         |
| Others                         |                                        |                |
| Survival status                |                                        | 455 252 55.4   |
| Alive                          |                                        | 203 44.6       |
| Dead                           |                                        | 184 90.6       |
| Dead by cancer                 |                                        |                |

Abbreviations: ASA, American Society of Anesthesiology; ECOG PS, Eastern Cooperative Oncology Group performance status; IFN, interferon; IL, interleukin; VEGF, vascular endothelial growth factor.

Univariate analysis showed associations between 5-year OS and CSS and the presence of ECOG-PS ≥ 1 (P = .005 and P = .007), ASA classification 3-4 (P < .0001 for both), pT3-4 (P = .019 and P = .009), pN1 (P = .001 and P < .0001), Fuhrman ≥ 3 (P = .010 and P = .008), necrosis (P = .024 and P = .016), perirenal fat invasion (P < .0001 for both), Hb < 11 g/dL (P = .001 and P = .002), multiple metastases (P = .002 and P = .001), and ≥ 2 involved organs (P = .002 and P = .005).

The median OS and CSS were both 43 months in the presence of a single metastasis and 16 months and 20 months, respectively, for multiple metastases. Two-year OS and CSS were 67% and 70% for single metastasis, and 44% and 45% for multiple metastases, respectively (hazard ratio [HR] for OS: 1.94, 95% CI, 1.28 to 2.95, P = .002 and HR for CSS: 2.07, 95% CI, 1.33 to 3.23, P = .001) (Fig 2).

The median OS and CSS were 30 months and 33 months, respectively, for patients with metastasis in a single organ and were both 14 months for patients with ≥ 2 involved organs. Two-year OS and CSS were 55% and 56% for patients with metastasis in a single organ and 36% and 38% for patients with metastases in multiple organs, respectively (HR for OS: 1.67, 95% CI, 1.21 to 2.32, P = .002).
| Variables                  | All Cases (N = 530) | Single (n = 111) | Multiple (n = 340) | P    |
|----------------------------|---------------------|------------------|-------------------|------|
| Age, years                 |                     |                  |                   |      |
| Median (range)             | 61 (23-94)          | 63 (40-90)       | 61 (23-94)        | .295 |
| Age, years                 |                     |                  |                   | .544 |
| ≤ 65                       | 267 (63.4)          | 64 (61)          | 203 (64.2)        |      |
| > 65                       | 154 (36.6)          | 41 (39)          | 113 (35.8)        |      |
| Sex                        |                     |                  |                   | .080 |
| Male                       | 300 (66.8)          | 81 (73.6)        | 219 (64.6)        |      |
| Female                     | 149 (33.2)          | 29 (26.4)        | 120 (35.4)        |      |
| BMI, kg/m²                 |                     |                  |                   | .018 |
| < 25                       | 125 (44.3)          | 29 (33.7)        | 96 (49)           |      |
| ≥ 25                       | 157 (55.7)          | 57 (66.3)        | 100 (51)          |      |
| ECOG PS                    |                     |                  |                   | .076 |
| 0                          | 40 (13)             | 11 (20.4)        | 29 (11.4)         |      |
| ≥ 1                        | 268 (87)            | 43 (79.6)        | 225 (88.6)        |      |
| ASA                        |                     |                  |                   | .330 |
| 1-2                        | 203 (68.6)          | 66 (72.5)        | 137 (66.8)        |      |
| 3-4                        | 93 (31.4)           | 25 (27.5)        | 68 (33.2)         |      |
| Symptoms                   |                     |                  |                   | .552 |
| No                         | 80 (19.2)           | 17 (17.2)        | 63 (19.9)         |      |
| Yes                        | 336 (80.8)          | 82 (82.8)        | 254 (80.1)        |      |
| Size, pT                   |                     |                  |                   | .196 |
| ≤ 7 cm                     | 109 (39.6)          | 41 (45.1)        | 68 (37)           |      |
| > 7 cm                     | 166 (60.4)          | 50 (54.9)        | 116 (63)          |      |
| Stage, pN                  |                     |                  |                   | .010 |
| pN0                        | 136 (68.7)          | 54 (80.6)        | 82 (62.6)         |      |
| pN1                        | 62 (31.3)           | 13 (19.4)        | 49 (37.4)         |      |
| Fuhrman                    |                     |                  |                   | .008 |
| 1-2                        | 81 (37)             | 26 (53.1)        | 55 (32.4)         |      |
| 3-4                        | 138 (63)            | 23 (46.9)        | 115 (67.6)        |      |
| Perirenal fat invasion     |                     |                  |                   | .019 |
| No                         | 179 (59.9)          | 63 (70)          | 116 (55.5)        |      |
| Yes                        | 120 (40.1)          | 27 (30)          | 93 (44.5)         |      |
| Renal vein invasion        |                     |                  |                   | .857 |
| No                         | 210 (71.2)          | 64 (71.9)        | 146 (70.9)        |      |
| Yes                        | 85 (28.8)           | 25 (28.1)        | 60 (29.1)         |      |
| Necrosis                   |                     |                  |                   | < .0001 |
| No                         | 170 (56.7)          | 66 (74.2)        | 104 (49.3)        |      |
| Yes                        | 130 (43.3)          | 23 (25.8)        | 107 (50.7)        |      |
| Histologic subtype         |                     |                  |                   | .372 |
| Clear cell                 | 247 (92.5)          | 86 (95.6)        | 161 (91)          |      |
| Papillary                  | 7 (2.6)             | 1 (1.1)          | 6 (3.4)           |      |
| Unclassified               | 13 (4.9)            | 3 (3.3)          | 10 (5.6)          |      |

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and HR for CSS: 1.62, 95% CI, 1.15 to 2.27, \( P = .005 \) (Fig 3).

The comparison of patients with bone metastasis (BM) versus lung metastasis (LM) revealed that the median OS and CSS for patients with BM were both not reached, whereas for LM both were 21 months. The 2-year OS and CSS were both 70% for patients with BM, and 45% and 47%, respectively, for patients with LM (HR for OS: 2.10, 95% CI, 1.14 to 3.88, \( P = .017 \) and HR for CSS: 2.03, 95% CI, 1.10 to 3.76, \( P = .024 \)) (Fig 4). The comparison of patients with BM (nonvertebral) versus BM (vertebral) revealed that the median OS and CSS were both not reached for patients with nonvertebral BM and were both 14 months for patients with vertebral BM. The 2-year OS and CSS were 75% and 45%, respectively, for both groups (HR: 3.61, 95% CI, 1.00 to 12.98, \( P = .035 \)) (Fig 5).

The comparison of patients with \( \leq 5 \) versus \( > 5 \) LM showed that the median OS and CSS were 30 and 11 months, respectively. The 2-year OS and CSS were 62% and 27% (HR: 3.21, 95% CI, 1.47 to 7.00, \( P = .003 \)) for both groups, respectively (Fig 6). The median OS according to the number of LM was stratified into three groups: 2-5 metastases, 33 months; 6-10 metastases, 14 months; and \( > 10 \) metastases, 7 months. Two-year OS was 67%, 47%, and 0% (Fig 7). Both median 5-year OS and median 5-year CSS according to the number of involved organs were as follows: one organ, 33 months; two organs, 15 months; and three or four organs, 7 months. The median OS of patients with \( > 10 \) LM versus \( \leq 2 \) metastatic organ sites was 7 and 14 months, and 2-year OS was 0% and 37%, respectively (HR: 1.96, 95% CI, 0.99 to 3.88, \( P = .043 \)) (Fig 8).

The median OS was 33 months for patients who received systemic therapy (immunotherapy or targeted therapy) and 10 months for those who did not; the median CSS was 41 and 12 months, respectively. Two-year OS was 60% and 38% (HR: 2.17, 95% CI, 1.46 to 3.23, \( P < .0001 \)) for those who received versus those who did not receive systemic therapy, whereas 2-year CSS was 60% and 40%, respectively (HR: 2.18, 95% CI, 1.45 to 3.28, \( P < .0001 \)) (Fig 9). The median OS was 24 months for patients who received only local treatment of the metastatic sites (radiotherapy and/or surgery).

In multivariate analysis, ASA 3-4 was an independent prognostic factor of 5-year OS (HR: 1.64, 95% CI, 1.08 to 2.49, \( P = .020 \)). Other independent prognostic factors of 5-year OS and CSS were perirenal fat invasion (HR: 2.02, 95% CI, 1.32 to 3.09, \( P = .001 \) and HR: 2.21, 95% CI, 1.40 to 3.47, \( P = .001 \)) and the presence of \( \leq 2 \) metastatic organ sites (HR: 2.19, 95% CI, 1.43 to 3.34, \( P < .0001 \) and HR: 2.01, 95% CI, 1.27 to 3.19, \( P = .003 \)) (Table 4).

We created a risk group stratification according to the variables which were significantly associated with OS in the multivariable analysis: perirenal fat invasion, \( \leq 2 \) metastatic organ sites, and presence of ASA classification 3-4 at the time of surgery.

When there were no adverse risk factors (favorable group), the median OS was not reached. When one adverse factor was present, the median OS was 33 months (intermediate group; HR: 2.04; 95% CI, 1.14 to 3.65; \( P = .016 \)). When two or three adverse factors were present (poor risk group), the median OS was 14 months (HR: 3.58; 95% CI, 2.02 to 6.34, \( P < .0001 \)) (Fig 10).

The model using risk stratification was more parsimonious than the multivariable model with a similar value of the Bayesian information criterion (1,005.9 vs 1,009.2, respectively).

### Table 2

Association of Demographic and Clinical-Pathological Variables With Single Versus Multiple Metastases in Renal Cell Carcinoma (Continued)

| Variables | All Cases (N = 530) | Single (n = 111) | Multiple (n = 340) | \( P \) |
|-----------|-------------------|-----------------|------------------|-------|
| Histological subtype | | | |
| Clear cell | 247 (84.3) | 86 (90.5) | 161 (81.3) | 0.042 |
| No-clear cell | 46 (15.7) | 9 (9.5) | 37 (18.7) | |
| Sarcomatoid features | | | | 0.270 |
| No | 179 (82.5) | 43 (87.8) | 136 (81) | |
| Yes | 38 (17.5) | 6 (12.2) | 32 (19) | |
| Hemoglobin, g/dL | | | | 0.007 |
| < 11 | 107 (33.3) | 20 (22) | 87 (37.8) | |
| \( \geq 11 \) | 214 (66.7) | 71 (78) | 143 (62.2) | |

Abbreviations: ASA, American Society of Anesthesiology; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status.
| Variable                  | All Cases (N = 530) | 1 Organ (n = 321) | ≥ 2 Organs (n = 166) | P  |
|---------------------------|---------------------|-------------------|----------------------|----|
| Age, years                |                     |                   |                      |    |
| Median (range)            | 61 (23-94)          | 62 (23-91)        | 60 (23-94)           | .179|
| Age, years                |                     |                   |                      | .555|
| ≤ 65                      | 287 (63.8)          | 184 (62.8)        | 103 (65.6)           |    |
| > 65                      | 163 (36.2)          | 109 (37.2)        | 54 (34.4)            |    |
| Sex                       |                     |                   |                      | .507|
| Male                      | 327 (67.4)          | 219 (68.4)        | 108 (65.5)           |    |
| Female                    | 158 (32.6)          | 101 (31.6)        | 57 (34.5)            |    |
| BMI, kg/m²                |                     |                   |                      | .002|
| < 25                      | 135 (46.2)          | 75 (39.5)         | 60 (58.8)            |    |
| ≥ 25                      | 157 (53.8)          | 115 (60.5)        | 42 (41.2)            |    |
| ECOG PS                   |                     |                   |                      | .004|
| 0                         | 58 (17.2)           | 48 (21.3)         | 10 (8.9)             |    |
| ≥ 1                       | 279 (82.8)          | 177 (78.7)        | 102 (91.1)           |    |
| ASA                       |                     |                   |                      | .898|
| 1-2                       | 213 (68.5)          | 145 (68.7)        | 68 (68)              |    |
| 3-4                       | 98 (31.5)           | 66 (31.3)         | 32 (32)              |    |
| Symptoms                  |                     |                   |                      | .569|
| No                        | 96 (21.4)           | 65 (22.2)         | 31 (19.9)            |    |
| Yes                       | 353 (78.6)          | 228 (77.8)        | 125 (80.1)           |    |
| Size, pT                  |                     |                   |                      | .947|
| ≤ 7 cm                    | 119 (39.3)          | 83 (39.2)         | 36 (39.6)            |    |
| > 7 cm                    | 184 (60.7)          | 129 (60.8)        | 55 (60.4)            |    |
| Stage, pN                 |                     |                   |                      | .001|
| pN0                       | 155 (69.5)          | 120 (75.9)        | 35 (53.8)            |    |
| pN1                       | 68 (30.5)           | 38 (24.1)         | 30 (46.2)            |    |
| Fuhrman                   |                     |                   |                      | .764|
| 1-2                       | 89 (35.7)           | 65 (36.3)         | 24 (34.3)            |    |
| 3-4                       | 160 (64.3)          | 114 (63.7)        | 46 (65.7)            |    |
| Perirenal fat invasion    |                     |                   |                      | .139|
| No                        | 202 (61.2)          | 148 (63.8)        | 54 (55.1)            |    |
| Yes                       | 128 (38.8)          | 84 (36.2)         | 44 (44.9)            |    |
| Renal vein invasion       |                     |                   |                      | .042|
| No                        | 233 (71.7)          | 171 (75)          | 62 (63.9)            |    |
| Yes                       | 92 (28.3)           | 57 (25)           | 35 (36.1)            |    |
| Necrosis                  |                     |                   |                      | .575|
| No                        | 194 (59)            | 135 (60)          | 59 (56.7)            |    |
| Yes                       | 135 (41)            | 90 (40)           | 45 (43.3)            |    |
| Histologic subtype        |                     |                   |                      | .096|
| Clear cell                | 274 (92.6)          | 202 (93.5)        | 72 (90)              |    |
| Papillary                 | 8 (2.7)             | 7 (3.2)           | 1 (1.3)              |    |
| Unclassified              | 14 (4.7)            | 7 (3.2)           | 7 (8.8)              |    |

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DISCUSSION

Data concerning the natural history and treatment-related outcomes among mRCC in Latin America are lacking. In our cohort, the prevalence of mRCC (de novo) was 14.5%, which is less than the prevalence rate of 20%-30% reported in the literature.3-7 However, this may be an underestimation since our cohort consisted of mostly of patients who had received nephrectomy—it is possible that many patients with mRCC may be treated by a medical oncologist exclusively. Our study identified ASA classification 3-4, perirenal fat invasion, and ≥ 2 metastatic organ sites as independent predictors of 5-year OS. Of critical importance, these are simple variables that are easily discerned in a urology practice in low- and middle-income countries when a cytoreductive nephrectomy is performed.

Most metastases were multiple at the time of presentation, with the lungs being the most commonly affected organs, followed by bone, lymph nodes, and liver, as in the literature.8,9 In roughly half of the cases, metastases involved a single site (51%). Bianchi et al8 reviewed 11,157 patients with mRCC from the Nationwide Inpatient Sample cohort and found that 61% were affected with metastasis in a single organ.

In our series, the increased percentage of patients with multiple metastases (75.4%) and with ≥ 2 metastatic sites (49%) could be responsible for the high mortality (44.6%) over a relatively short follow-up. Our 2-year OS, however, was similar to that reported by others.10,11

Interestingly, a BMI of ≥ 25 kg/m² was associated with single metastases and with single-organ involvement in our cohort, so being overweight was a protective factor. In our results, the OS rates were 41 months for ≥ 25 kg/m² BMI versus 25 months for < 25 kg/m² BMI. The International Metastatic Renal Cell Carcinoma Database Consortium informed that being overweight was associated with a better response to treatment.14 Our results indicate that BMI is a variable that should be more extensively studied.

Abbreviations: ASA, American Society of Anesthesiology; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status.

![FIG 1. OS for the entire patient cohort. OS, overall survival.](image-url)
There are many predictive models of progression-free survival and OS in mRCC. Although some stress the prognostic value of the metastatic sites, others report that the number of metastases is more relevant. In our cohort, patients with multiple metastases had almost twice the risk of death compared with patients with single metastases. As to the number of metastatic sites involved, it has been reported that having more than one metastatic

**FIG 2.** OS and CSS in relation to the presence of a single metastasis versus multiple metastases. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.

**FIG 3.** OS and CSS in relation to the metastasis in a single-organ versus metastatic involvement of two or more organs. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.
site increases the risk of death by 20%-50%.\textsuperscript{15,18,19} Han et al\textsuperscript{20} showed that patients with disease in multiple organ sites fare worse than patients with disease limited to either lung or bone with a median survival of 11, 27, and 27 months, and the risk of death was two times greater for multiple metastatic sites. Our results are similar with twice the risk of death for the group of patients with $\geq 2$ metastatic sites.

**FIG 4.** OS and CSS in relation to the presence of bone versus lung metastasis. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.

**FIG 5.** OS and CSS in relation to the presence of nonvertebral versus vertebral bone metastasis. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.
In most series, patients with BM and liver metastases have a worse prognosis in comparison to LM. Leibovich et al reported that patients with BM have a 35% higher risk of mortality because of RCC and that patients with liver metastases have a 69% higher risk of mortality because of RCC compared with patients with metastatic disease in

**FIG 6.** OS and CSS in relation to the presence of ≤ 5 versus > 5 lung metastases. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.

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other organs. Other studies did not find a difference in survival rates of patients with BM versus LM.\textsuperscript{20,21} Series including patients treated with targeted therapies and cytokines, however, confirmed that the presence of BM implies a worse prognosis.\textsuperscript{22,23} A peculiar finding of our study is that patients with BM had a better survival than

FIG 8. OS and CSS in relation to the presence of > 10 lung metastases versus metastatic involvement of two or more organs. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.

FIG 9. OS and CSS in relation to the receipt of systemic therapy (IT and targeted therapy). CSS, cancer-specific survival; HR, hazard ratio; IT, immunotherapy; OS, overall survival; ST, systemic treatment; VEGF, vascular endothelial growth factor.
those with LM, and we are yet to ascertain the reasons for this. We did not have biopsy confirmation of the BM in most patients (60%), and only radiologic and clinical information was used; nevertheless, within confirmed cases, the differences in favor of BM were maintained. Notwithstanding, we found that the location of the BM was important; there was a threefold increase in the risk of death for patients with vertebral BM. In addition, we found that nonvertebral bone metastases were associated with a better prognosis than oligometastases in the lungs.

The lungs were the most common metastatic site in our series, and the higher the number of lesions, the worse the prognosis, which was very poor when there were > 10 lung metastases. When patients were grouped according to the number of lung metastases, the median OS and CSS were similar to those seen with grouping by the number of affected organs.

Targeted systemic therapies have been associated with increased progression-free survival and OS in mRCC.24 In our series, systemic therapy conferred a significant benefit, both in OS and in CSS. A limited number of patients 177 (34%) received systemic treatments; however, as patients were treated from 1990 to 2015, most received either interferon or anti–vascular endothelial growth factor drugs. In respect to immunotherapy considerations, as our cohort in this publication encompassed patients treated up to 2015, the use of the newer immune checkpoint inhibitor (ICI) drugs was not available. In future publications, the use of the newer ICIs will be contemplated.

Nephrectomy before systemic therapy may improve survival25-27 or not.28 Since the publication of the CAR-MENA trial,28 the role of cytoreductive nephrectomy is being challenged. In our series, the impact of cytoreductive nephrectomy in mRCC could not be ascertained since almost all patients were treated with nephrectomies. In

### Table 4. Cox Regression Analysis for OS and CSS

| Variable                          | Univariate HR (95% CI) | P      | Multivariate HR (95% CI) | P      | Univariate HR (95% CI) | P      | Multivariate HR (95% CI) | P      |
|-----------------------------------|------------------------|--------|--------------------------|--------|------------------------|--------|--------------------------|--------|
| ASA (3-4 v 1-2)                   | 1.88 (1.37 to 2.57)    | <.0001 | 1.64 (1.08 to 2.49)      | .02    | 1.81 (1.31 to 2.50)    | <.0001 | 1.40 (0.89 to 2.21)      | .138   |
| Size pT (> 7 cm v ≤ 7 cm)         | 1.61 (1.08 to 2.41)    | .019   | 1.17 (0.74 to 1.86)      | .481   | 1.77 (1.15 to 2.73)    | .009   | 1.25 (0.76 to 2.07)      | .367   |
| Perirenal fat invasion            | 1.87 (1.31 to 2.67)    | <.0001 | 2.02 (1.32 to 3.09)      | .001   | 2.06 (1.42 to 2.99)    | <.0001 | 2.21 (1.40 to 3.47)      | .001   |
| M+ (≥ 2 org. v < 2 org.)          | 1.67 (1.21 to 1.32)    | .002   | 2.19 (1.43 to 3.34)      | <.0001 | 1.62 (1.15 to 2.27)    | .005   | 2.01 (1.27 to 3.19)      | .003   |

Abbreviations: ASA, American Society of Anesthesiology; CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.

FIG 10. OS according to three risk groups. ASA, American Society of Anesthesiology; HR, hazard ratio; NR, no response; OS, overall survival.
multivariate analyses, ASA 3-4, perirenal fat invasion, and ≥ 2 metastatic organ sites were an independent prognostic factor of 5-year OS. The ASA and the number of involved organs were associated with worse survival in the literature. The involvement of perirenal fat has been shown to affect the results of a series of both radical and partial nephrectomies. Although current management of mRCC has evolved, we believe that our prognostic data are valid, especially regarding cases in which a cytoreductive nephrectomy is indicated.

To our knowledge, we reported for the first time the role of prognostic factors in a large international cohort of patients with de novo mRCC in Latin America. The Latin American Renal Cancer Group is active in growing and enhancing its database, and the affiliated centers keep sending in new cases. Recently, data and biological materials from some of our centers’ tissue banks were made available for collaborative projects with North American institutions, such as the National Cancer Institute.

Our study has several limitations inherent to its retrospective nature. Additionally, the absence of central pathology review limits our assessment of certain elements such as sarcomatoid histology and other nonclear cell subtypes. Treatment discrepancies among different centers might have led to variations in clinical presentation, surgical technique, and patient adherence to follow up. As our analyses were performed before the publication of the CARMENA and SURTIME trials, cytoreductive nephrectomies were the rule, which is not the case anymore. Finally, modern ICI therapies were not available at the time of this study, which may limit the applicability of our findings.

In conclusion, in mRCC, perirenal fat invasion and ≥ 2 metastatic sites predicted shorter OS and CSS; ASA 3-4 was an independent predictor of poor OS. Patients with nonvertebral BM had a better prognosis compared with those with LM. Systemic treatments were associated with better survival rates. External validation of these data could lead to a simple and straightforward prognostic tool for patients with de novo mRCC.

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**DISCLAIMER**

Our research is observational, does not involve participation of humans in any kind of experiment, and preserves patients identifications.

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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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REFERENCES
1. Znaor A, Lortet-Tieulent J, Laversanne M, et al: International variations and trends in renal cell carcinoma incidence and mortality. Eur Urol 67:519-530, 2015
2. Ferlay J, Soerjomataram I, Dikshit R, et al: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E395-E396, 2015
3. Ferlay J, Parkin DM, Steliarova-Foucher E: Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 46:765-781, 2010
4. Sun M, Thuret R, Abdollah F, et al: Age-adjusted incidence, mortality, and survival rates of stage-specific renal cell carcinoma in North America: A trend analysis. Eur Urol 59:135-141, 2011
5. Moch H, Humphrey PA, Ulbright TM, et al: WHO Classification of Tumours of the Urinary System and Male Genital Organs. Lyon, France, International Agency for Research on Cancer, 2016
6. Kane CJ, Mallin K, Ritchey J, et al: Renal cell cancer stage migration: Analysis of the National Cancer Data Base. Cancer 113:78-83, 2008
7. Dabestani S, Thorstenson A, Lindblad P: Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: A population-based study. World J Urol 34:1081-1086, 2016
8. Bianchi M, Sun M, Jeldres C, et al: Distribution of metastatic sites in renal cell carcinoma: A population-based analysis. Ann Oncol 23:973-980, 2012
9. Saïto H, Nakayama M, Nakamura K, et al: Distant metastasis of renal adenocarcinoma in nephrectomized cases. J Urol 127:1092-1095, 1982
10. Heng DY, 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 27:5794-5799, 2009
11. Yu X, Guo G, Li X: Retrospective analysis of the efficacy and safety of sorafenib in Chinese patients with metastatic renal cell carcinoma and prognostic factors related to overall survival. Medicine 94:e1361, 2015
12. Capitanio U, Jeldres C, Patard JJ, et al: Stage-specific effect of nodal metastases on survival in patients with non-metastatic renal cell carcinoma. BJU Int 103:33-37, 2009
13. Josslyn SA, Srintrapun SJ, Konety BR: Impact of lymphadenectomy and nodal burden in renal cell carcinoma: Retrospective analysis of the National Surveillance, Epidemiology, and End Results database. Urology 65:675-680, 2005
14. Albiger L, Ari Hakimi A, Xie W, et al: Body mass index and metastatic renal cell carcinoma: Clinical and biological correlations. J Clin Oncol 34:3655-3663, 2016
15. Elson P, Witte R, Trump DL: Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. Cancer Res 48:7310-7313, 1988
16. Motzer RJ, Mazumdar M, Bacik J, et al: Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 17:2530-2540, 1999
17. Leibovich BC, Cheville JC, Lohe CM, et al: A scoring algorithm to predict survival for patients with metastatic clear cell renal cell carcinoma: A stratification tool for prospective clinical trials. J Urol 174:1759-1763, 2005, discussion 1763
18. Negrier S, Escudier B, Gomez F, et al: Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: A report from the Groupe Francais d’Immunotherapie. Ann Oncol 13:1460-1468, 2002
19. Escudier B, Choueiri TK, Oudard S, et al: Prognostic factors of metastatic renal cell carcinoma after failure of immunotherapy: New paradigm from a large phase III trial with shark cartilage extract AE 941. J Urol 178:1901-1905, 2007
20. KR Han, AJ Pantuck, MH Bui, et al: Number of metastatic sites rather than location dictates overall survival of patients with node negative metastatic renal cell carcinoma. Urology 61:314, 2003
21. Tsuda S, Koga S, Nishikido M, et al: Evaluation of bone metastases from renal cell carcinoma. Hinyokika Kyo 47:155-158, 2001
22. Patil S, Figlin RA, Hutson TE, et al: Prognostic factors for progression-free and overall survival with sunitinib targeted therapy and with cytokine as first-line therapy in patients with metastatic renal cell carcinoma. Ann Oncol 22:295-300, 2011
23. McKay R, Kroeger N, Xie W, et al: Impact of bone and liver metastases on patients with renal cell carcinoma treated with targeted therapy. Eur Urol 65:577-584, 2014
24. Choueiri TK, Motzer RJ: Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med 376:354-366, 2017
25. Flanigan RC, Salmon SE, Blumenstein BA, et al: Nephrectomy followed by interferon alfa-2b alone for metastatic renal-cell carcinoma. N Engl J Med 345:1655-1659, 2001
26. Mickisch GH, Garin A, van Poppel H, et al: Radical nephrectomy plus interferon alpha based immunotherapy compared with interferon-alpha alone in metastatic renal-cell carcinoma. A randomized trial. Lancet 358:986-1070, 2001
27. Petrelli F, Coinu A, Vavassori I, et al: Cytoreductive nephrectomy in metastatic renal cell carcinoma treated with targeted therapies: A systematic review with a meta-analysis. Clin Genitourin Cancer 14:465-472, 2016
28. Méjean A, Ravaud A, Thezenas S, et al: Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 379:417-427, 2018
29. de Casio Zequi S, de Campos EC, Guimaraes GC, et al: The use of the American Society of Anesthesiology Classification as a prognostic factor in patients with renal cell carcinoma. Urol Int 84:67-72, 2010
30. Shah PH, Moreira DM, Patel VR, et al: Partial nephrectomy is associated with higher risk of relapse with radical nephrectomy for clinical stage T1 renal cell carcinoma pathologically up staged to T3a. J Urol 198:289-296, 2017