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

Diego Abreu, MD[1]; Gustavo Carvalhal, MD[2]; Guillermo Gueglio, MD[3]; Ignacio Tobia, MD[3]; Patricio Garcia, MD[3]; Alvaro Zuñiga, MD[4]; Luis Meza, MD[5]; Rubén Bengió, MD[6]; Carlos Scorticati, MD[7]; Ricardo Castillejos, MD[8]; Francisco Rodriguez, MD[8]; Ana María Autran, MD[9]; Carmen Gonzales, MD[9]; Jose Gadu, MD[10]; Alejandro Nolazco, MD[11]; Carlos Ameri, MD[12]; Hamilton Zampolli, MD[13]; Raúl Langenhin, MD[14]; Diego Muguruza, MD[14]; Marcos Tobías Machado, MD[15]; Pablo Mingote, MD[16]; Juan Yandian, MD[17]; Jorge Clavijo, MD[17]; Lucas Nogueira, MD[18]; Omar Clark, MD[19]; Fernando Secin, MD[20]; Agustín Rovegno, MD[20]; Ana Vilas, MD[21]; Enrique Barrios, MD[22]; Ricardo Decia, MD[1]; Gustavo Guimarães, MD[23]; Sidney Glina, MD[24]; Sumanta K. Pal, MD[25]; Oscar Rodriguez, MD[26]; Joan Palou, MD[26]; Philippe Spiess, MD[27]; Primo N. Lara Jr, MD[28]; W. Marston Linehan, MD[29]; Antonio Luigi Pastore, MD[30]; and Stenio C. Zequi, MD[23]

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.

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.[1-3] 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.[4] 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.

CONTEXT

Key Objective

Are prognostic factors in de novo metastatic renal cell cancer different in Latin American population than those reported in other international cohorts?

Knowledge Generated

A study from a multicentric, multinational cohort identified the American Society of Anesthesiology classification 3-4, perirenal fat invasion, and ≥ 2 metastatic organ sites as independent prognostic factors of 5-year overall survival in a setting where cytoreductive nephrectomy was the norm.

Relevance

We believe that these findings are useful to provide a simple tool for management decisions in a heterogeneous world region, where resources for systemic treatments are limited.

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/m^2 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%.

TABLE 1. Patients' Clinical and Pathologic Characteristics

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

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TABLE 1. Patients' Clinical and Pathologic Characteristics (Continued)

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

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, $P = .002$

TABLE 2. Association of Demographic and Clinical-Pathological Variables With Single Versus Multiple Metastases in Renal Cell Carcinoma

		Metastasis		
Variables	All Cases (N = 530)	Single (n = 111)	Multiple (n = 340)	P
Age, years				.295
Median (range)	61 (23-94)	63 (40-90)	61 (23-94)	
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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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
		Metastasis		
Histological subtype				.042
Clear cell	247 (84.3)	86 (90.5)	161 (81.3)	
No-clear cell	46 (15.7)	9 (9.5)	37 (18.7)	
Sarcomatoid features				.270
No	179 (82.5)	43 (87.8)	136 (81)	
Yes	38 (17.5)	6 (12.2)	32 (19)	
Hemoglobin, g/dL				.007
< 11	107 (33.3)	20 (22)	87 (37.8)	
≥ 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.

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 for both) (Fig 5).

The comparison of patients with ≤ 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 ≥ 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 vsersus 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 > 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, ≤ 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 v 1,009.2, respectively).

TABLE 3. Association of Demographic and Clinical-Pathologic Variables With Metastasis in 1 Organ Versus ≥ 2 Organs in Renal Cell Carcinoma

		Metastasis		
Variable	All Cases (N = 530)	1 Organ (n = 321)	≥ 2 Organs (n = 166)	P
Age, years				.179
Median (range)	61 (23-94)	62 (23-91)	60 (23-94)	
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/m^2				.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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TABLE 3. Association of Demographic and Clinical-Pathologic Variables With Metastasis in 1 Organ Versus ≥ 2 Organs in Renal Cell Carcinoma (Continued)

| | | Metastasis | | |
Variable	All Cases (N = 530)	1 Organ (n = 321)	≥ 2 Organs (n = 166)	P
Histologic subtype				.003
Clear cell	274 (84.8)	202 (88.6)	72 (75.8)	
No-clear cell	49 (15.2)	26 (11.4)	23 (24.2)	
Sarcomatoid features				.099
No	202 (82.1)	149 (84.7)	53 (75.7)	
Yes	44 (17.9)	27 (15.3)	17 (24.3)	
Hemoglobin, g/dL				.174
< 11	111 (32.3)	68 (29.8)	43 (37.1)	
≥ 11	233 (67.7)	160 (78)	73 (62.9)	

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

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 al[8] 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]

In our series, lymph node involvement (pN1) was associated with multiple metastases and with more than one metastatic site. In the literature, nodal dissemination is highly associated with the presence of distant metastases. Moreover, the 5-year survival in patients with distant metastases and positive lymph nodes is worse than that in patients with distant metastases and negative lymph nodes

(21% v 39.4%). When nodal metastases are present, 5-year OS ranges from 11% to 35%.[12,13]

Interestingly, a BMI of ≥ 25 kg/m^2 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/m^2 BMI versus 25 months for < 25 kg/m^2 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.
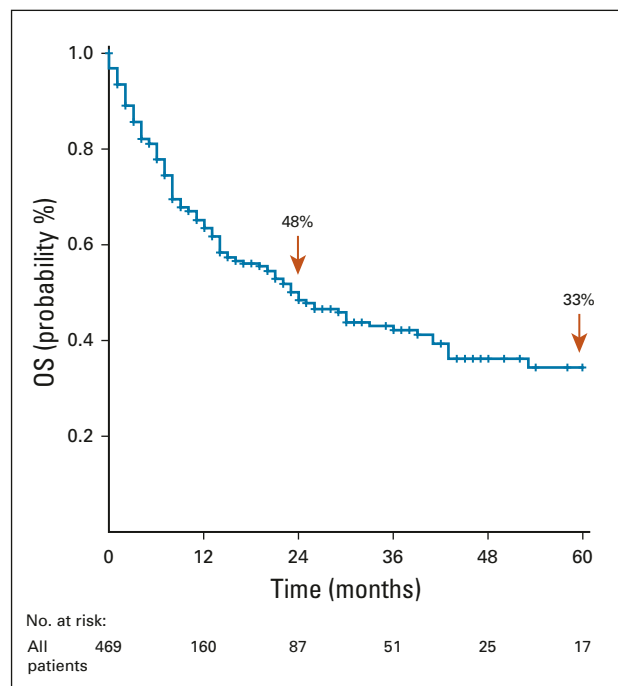

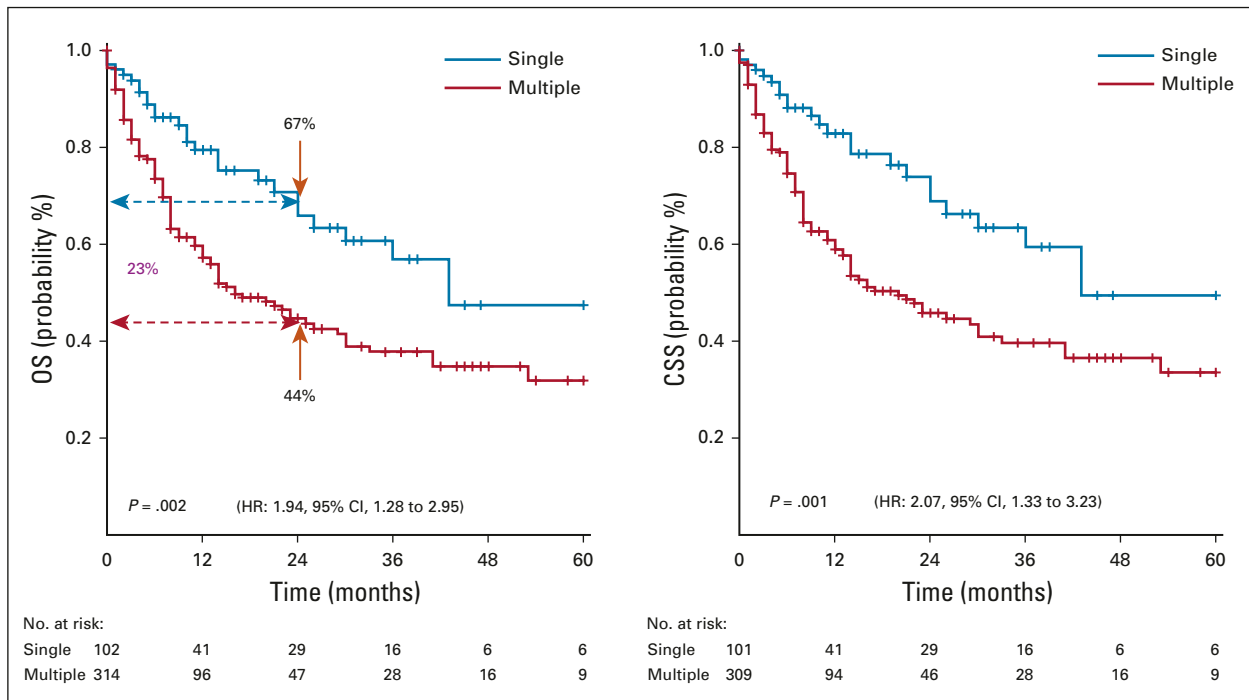**FIG 1.** OS for the entire patient cohort. OS, overall survival.

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.

There are many predictive models of progression-free survival and OS in mRCC.[10,15-19] Although some stress the prognostic value of the metastatic sites, others report that the number of metastases is more relevant.[15-20] 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
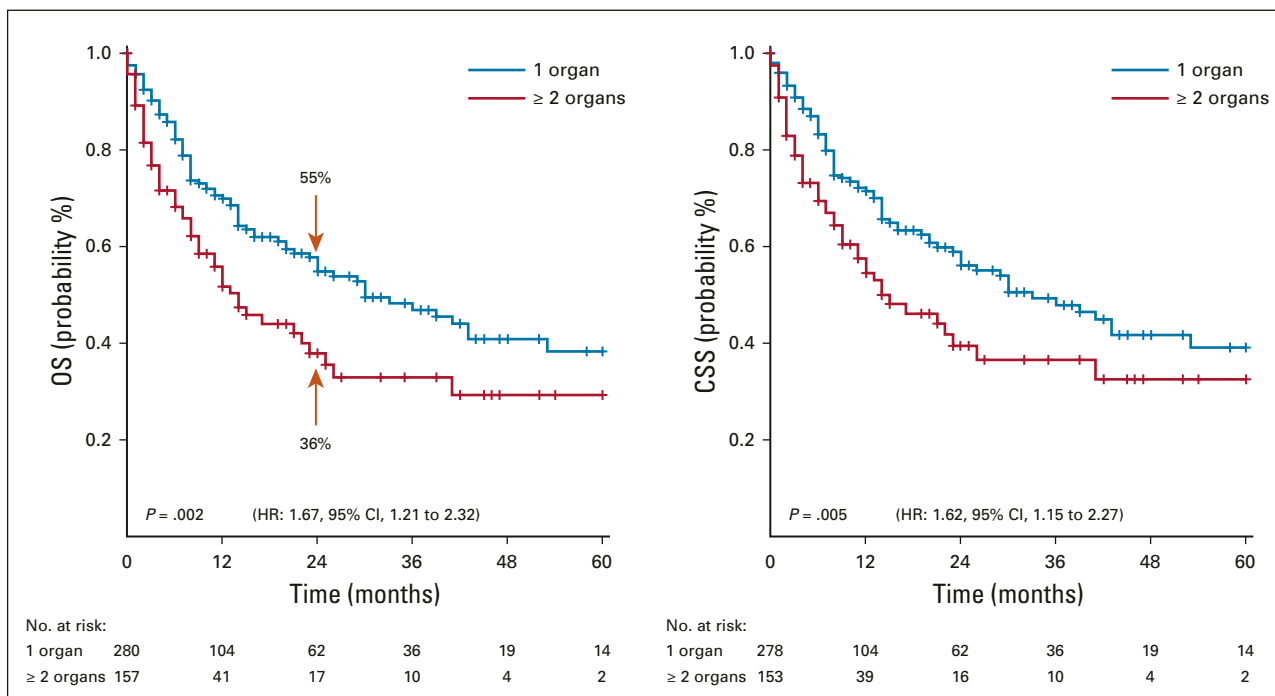
FIG 3. OS and CSS in relation to the metastasis in a single-organ versus metastatic involvement of two or more organs. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.
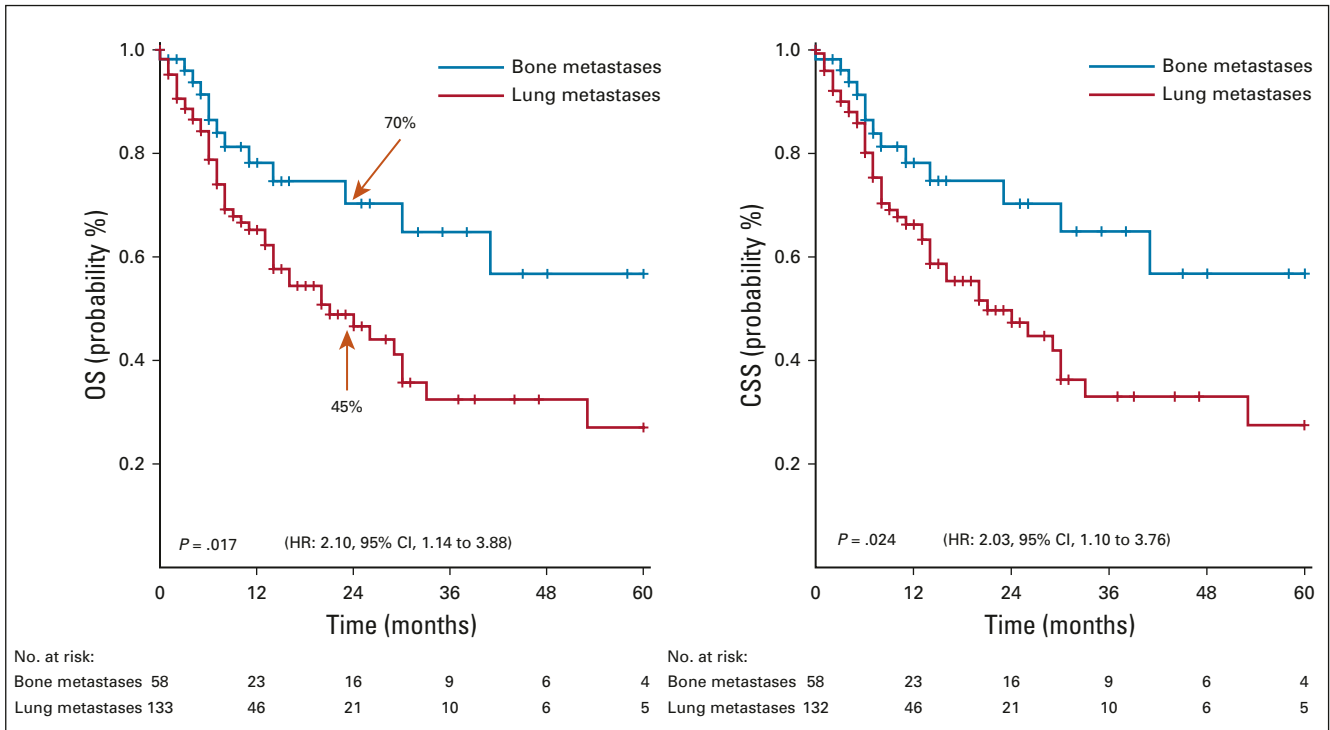
FIG 4. OS and CSS in relation to the presence of bone versus lung metastasis. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.

site increases the risk of death by 20%-50%.[15,18,19] Han et al[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 ≥ 2 metastatic sites.
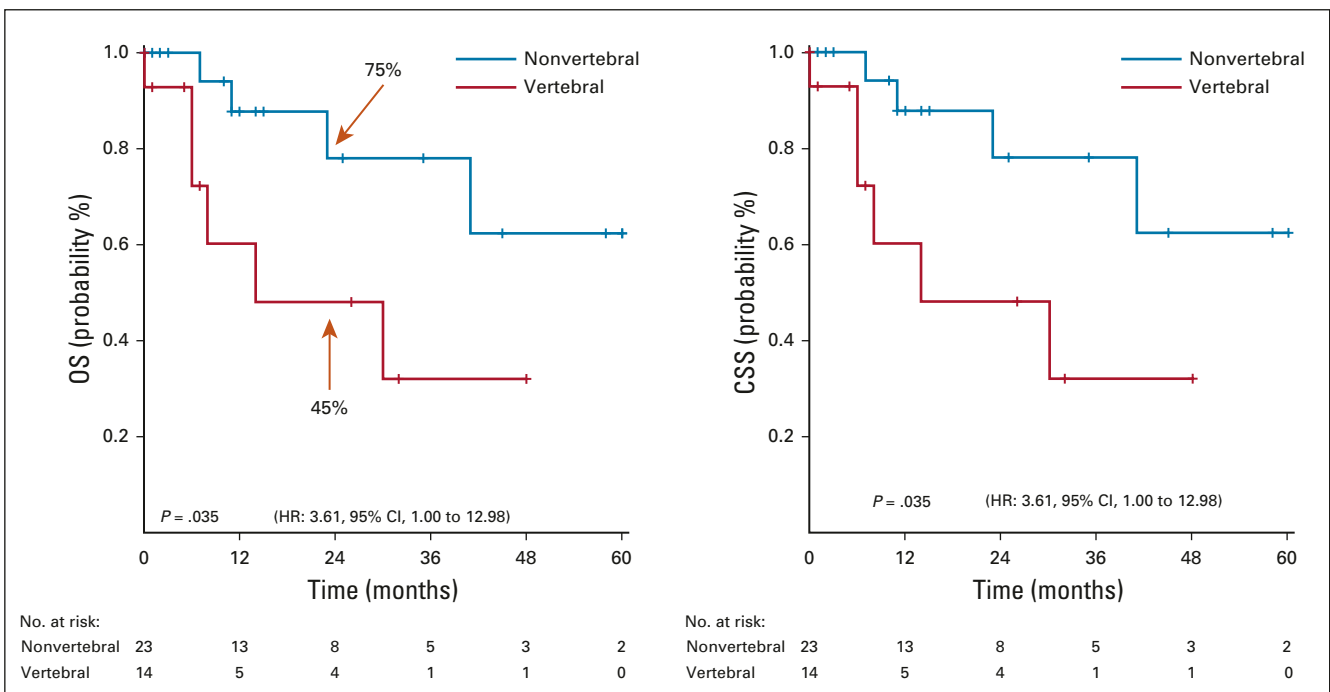
FIG 5. OS and CSS in relation to the presence of nonvertebral versus vertebral bone metastasis. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.
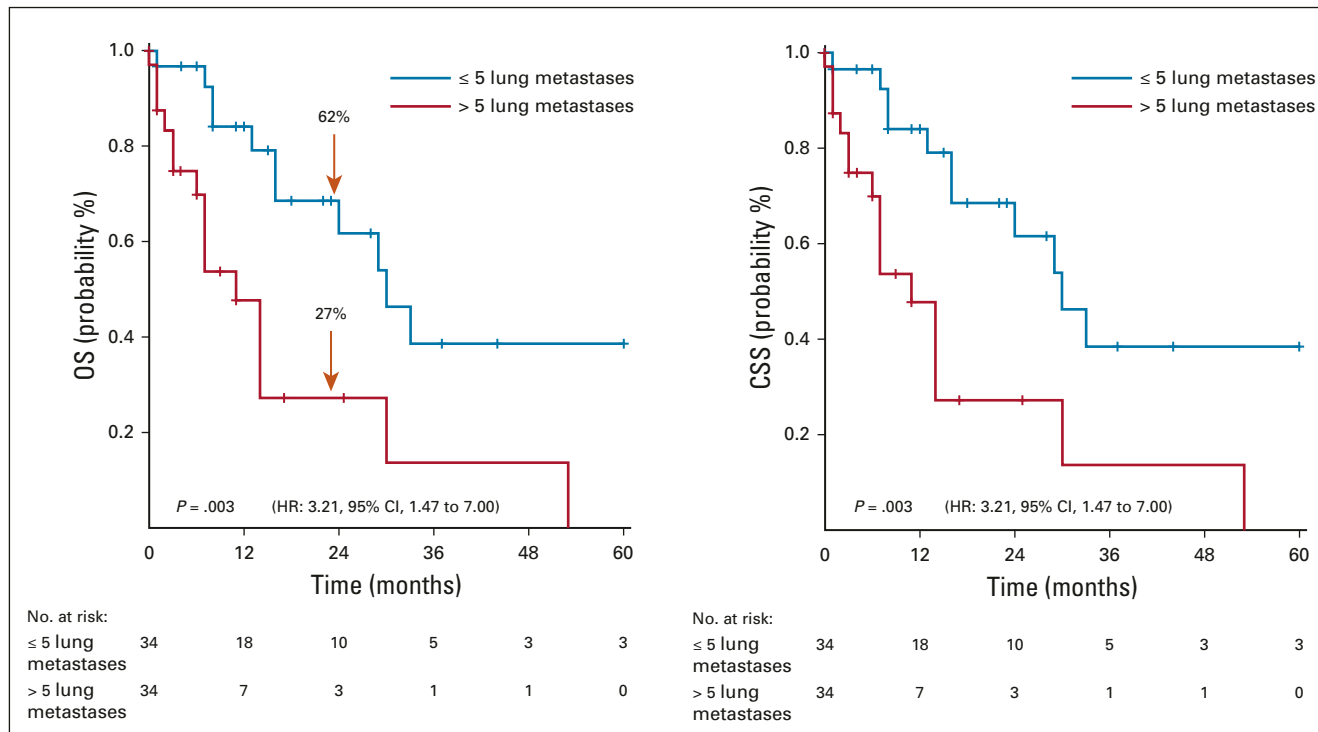
FIG 6. OS and CSS in relation to the presence of ≤ 5 versus > 5 lung metastases. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.

In most series, patients with BM and liver metastases have a worse prognosis in comparison to LM.[15,18,19] Leibovich et al[17] 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
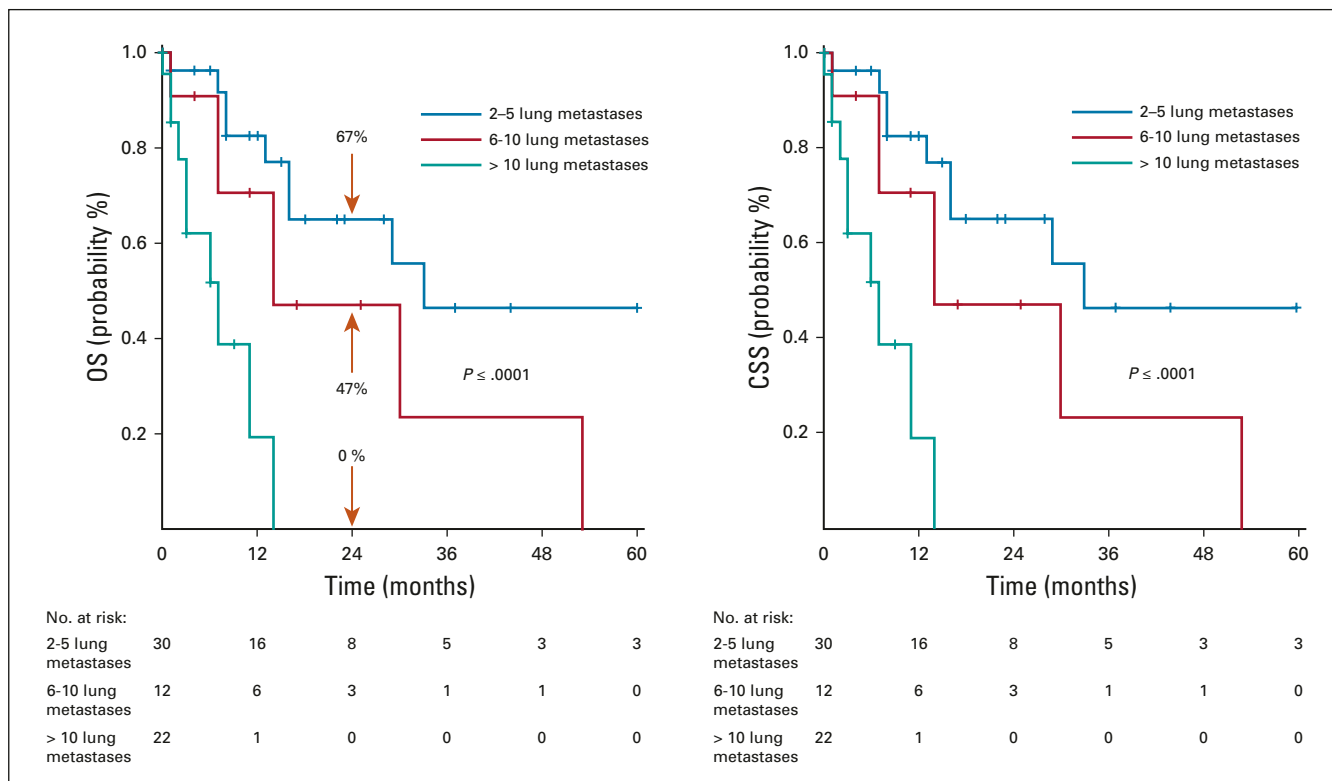
FIG 7. OS and CSS in relation to the number of lung metastases. CSS, cancer-specific survival; OS, overall survival.
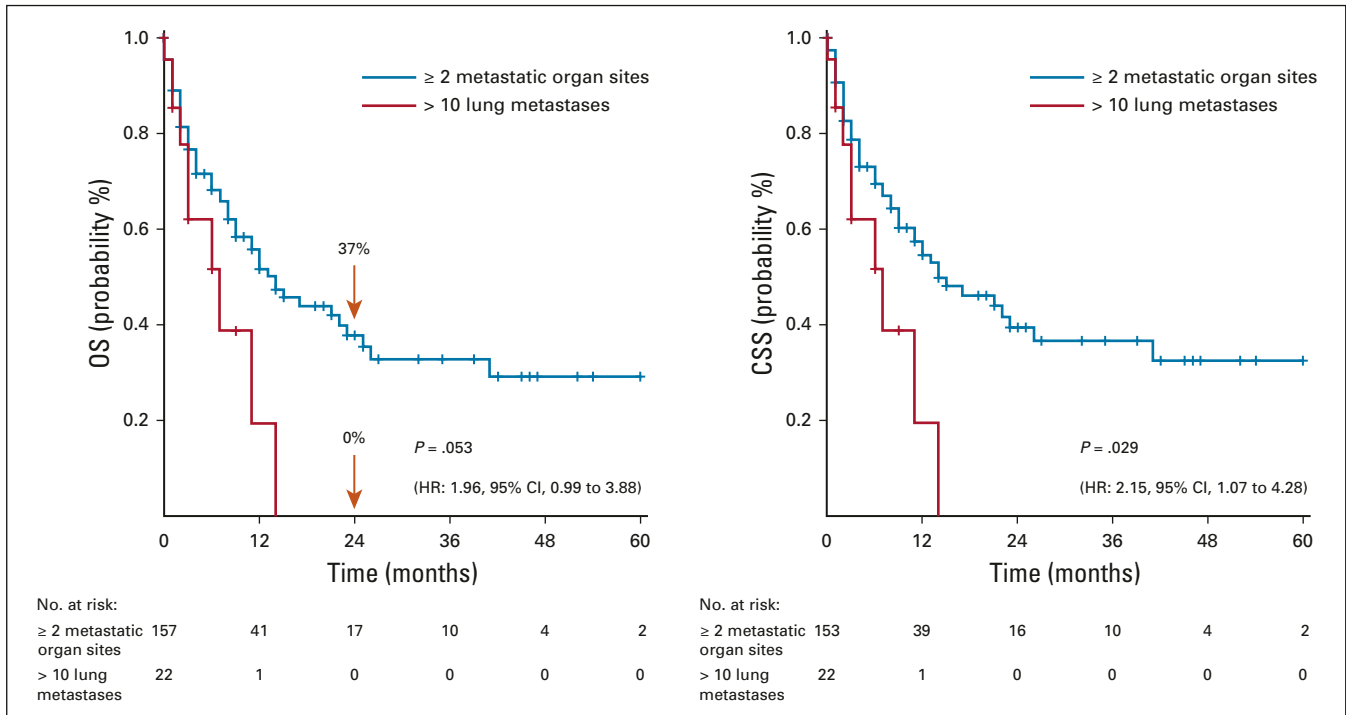
FIG 8. OS and CSS in relation to the presence of > 10 lung metastases versus metastatic involvement of two or more organs. CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.

other organs. Other studies did not find a difference in survival rates of patients with BM versus LM.[20,21] Series including patients treated with targeted therapies and cytokines, however, confirmed that the presence of BM implies a worse prognosis.[22,23] A peculiar finding of our study is that patients with BM had a better survival than
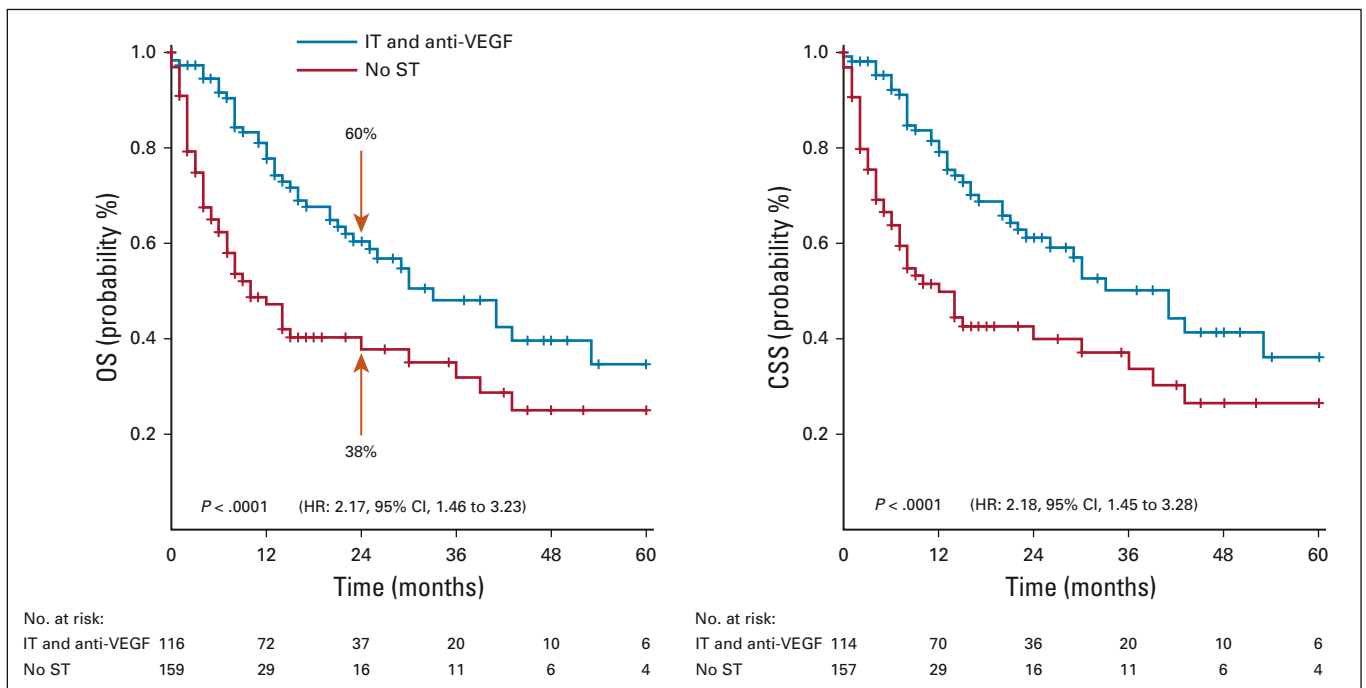
FIG 9. OS and CSS in relation to the receipt of systemic therapy (IT and targeted therapy). CSS, cancer-specific survival; HR, hazard ratio; IT, immunotherapy; OS, overall survival; ST, systemic treatment; VEGF, vascular endothelial growth factor.

TABLE 4. Cox Regression Analysis for OS and CSS

Variable	5-Year OS				5-Year CSS			
	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.

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 survival[25-27] 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
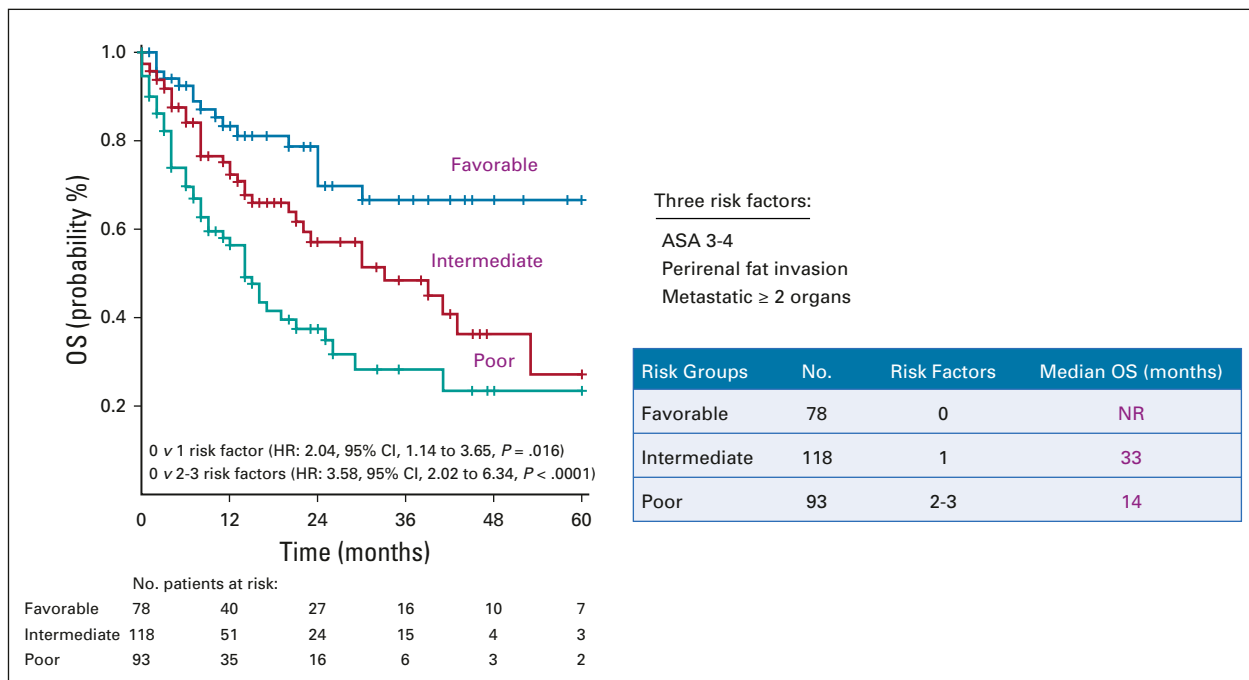

Three risk factors:

ASA 3-4
Perirenal fat invasion
Metastatic ≥ 2 organs

Risk Groups	No.	Risk Factors	Median OS (months)
Favorable	78	0	NR
Intermediate	118	1	33
Poor	93	2-3	14

0 v 1 risk factor (HR: 2.04, 95% CI, 1.14 to 3.65, P = .016)
0 v 2-3 risk factors (HR: 3.58, 95% CI, 2.02 to 6.34, P < .0001)

No. patients at risk:

Favorable	78	40	27	16	10	7
Intermediate	118	51	24	15	4	3
Poor	93	35	16	6	3	2

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[29] 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.[30] 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.

AFFILIATIONS

[1]Servicio de Urología, Hospital Pasteur, Montevideo, Uruguay
[2]Hospital São Lucas da PUCRS, Porto Alegre, Brazil
[3]Hospital Italiano, Buenos Aires, Argentina
[4]Universidad Católica, Santiago de Chile, Chile
[5]Instituto Nacional de Enfermedades Neoplásicas (INEN), Lima, Peru
[6]Clinica Profesor Bengio, Cordoba, Argentina
[7]Hospital de Clínicas, Buenos Aires, Argentina
[8]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCNSZ), Ciudad de México, Mexico
[9]Fundación Jiménez Díaz, Madrid, Spain
[10]Hospital Militar, Ciudad de México, Mexico
[11]Hospital Británico, Buenos Aires, Argentina
[12]Hospital Alemán, Buenos Aires, Argentina
[13]Instituto Arnaldo Vieira de Carvalho, São Paulo, Brazil
[14]Coperativa Médica de Paysandú (COMEPA), Paysandú, Uruguay
[15]Escuela de Medicina, ABC, São Paulo, Brazil
[16]Policlinico Neuquén, Neuquén, Argentina
[17]Hospital de Clínicas, Montevideo, Uruguay
[18]Universidade de Minas Gerais, Belo Horizonte, Brazil
[19]Hospital Militar, Montevideo, Uruguay
[20]Centro de Educación Médica e Investigaciones Clínicas (CEMIC), Buenos Aires, Argentina
[21]Departamento de Patología, Hospital Pasteur, Montevideo, Uruguay
[22]Departamento de Métodos Cuantitativos, Facultad de Medicina, Montevideo, Uruguay
[23]A.C. Camargo Cancer Center, São Paulo, Brazil
[24]Hospital Ipiranga, São Paulo, Brazil
[25]City of Hope, Duarte, CA
[26]Fundación Puigvert, Barcelona, Spain
[27]Lee Moffitt Cancer Center, Tampa, FL
[28]The University of California Davis Comprehensive Cancer Center, Sacramento, CA
[29]Center for Cancer Research, National Cancer Institute, Bethesda, MD
[30]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

CORRESPONDING AUTHOR

Diego Abreu, MD, Hospital Pasteur, Lombardia 6256, Montevideo CP 11500, Uruguay; e-mail: die.abreu@gmail.com.

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Francisco Rodriguez
Honoraria: Astellas Pharma, Bayer, Asofarma, Ferring, GlaxoSmithKline, Janssen-Cilag, Lilly, MSD Oncology
Consulting or Advisory Role: Astellas Pharma, Asofarma, GlaxoSmithKline, Janssen Oncology, MSD Oncology
Speakers' Bureau: Astellas Pharma, Asofarma, Bayer, Janssen Oncology, MSD Oncology
Travel, Accommodations, Expenses: Janssen Oncology, Asofarma

Jose Gadu
Speakers' Bureau: Janssen, Bayer

Hamilton Zampolli
Honoraria: Janssen Oncology
Consulting or Advisory Role: Janssen Oncology

Lucas Nogueira
Consulting or Advisory Role: Bayer
Speakers' Bureau: Bayer, Astellas Pharma

Agustin Rovegno
Employment: Abbott Laboratories
Honoraria: Baliarda SA

Sidney Glina
Honoraria: Pfizer

Sumanta K. Pal
Consulting or Advisory Role: Pfizer, Novartis, Aveo, Myriad Pharmaceuticals, Genentech, Exelixis, Bristol Myers Squibb, Astellas Pharma, Ipsen, Eisai

Philippe Spiess
Leadership: NCCN, Global Society of Rare Genitourinary Tumors
Honoraria: UpToDate
Other Relationship: NCCN
Uncompensated Relationships: Moffitt

Primo N. Lara
Consulting or Advisory Role: Janssen, Calithera Biosciences
Research Funding: Janssen Biotech, Merck, Pharmacyclics, Incyte, Taiho Pharmaceutical

Stenio C. Zequi
Consulting or Advisory Role: Pfizer, Astellas Brazil
Speakers' Bureau: Pfizer, Astellas Pharma, Bayer, Janssen, Astra Zeneca Brazil

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