Prognostic factors in Latin American patients with localized and advanced renal cell carcinoma: a literature review

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Background and Objective: Some countries in Latin America (LA) may have the greatest increase in the incidence of renal cell carcinoma (RCC) in both sexes in the coming decades, according to some projections. Increasing efforts to study prognostic factors related to RCC may shorten the regional discrepancies, particularly in the scenario of scarce literature in LA, in comparison to Europe or North America. The evaluation of RCC prognosis allows a greater capacity to anticipate outcomes, in addition to a better understanding of tumor biology and the orientation of the proposed treatment. Herein, we provide a review of the main prognostic factors described in different stages of the disease, considering the progress of publications on kidney cancer in LA.

Methods: The PubMed database was used to identify studies on this theme, particularly those from LA. Studies by the Latin American Renal Cancer Group (LARCG) and the Latin American Cooperative Oncology Group (LACOG) were included.

Key Content and Findings: Overall, tumor-related factors such as pathological stage, tumor size, nuclear grade, and histological subtype had the most important independent prognostic impact. Nevertheless,

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grouping these data with clinical, demographic, and biomolecular parameters can lead to a better prognosis analysis. Finally, the authors acknowledge the efforts of some nonprofit regional organizations in the activities and studies of RCC in different settings.

Conclusions: Anatomical and histological prognostic factors for RCC have been widely studied for decades. In recent years, biomolecular factors have attracted considerable attention.

Keywords: Prognostic factors; survival predictors; renal cell carcinoma (RCC); Latin America (LA)

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Introduction

Background

Renal cell carcinoma (RCC) accounts for more than 270,000 new cases in men and 160,000 in women (1). Recent projections indicate that some countries in Latin America (LA) require urgent planning of healthcare resources for the diagnosis and management of this cancer. Brazil and Ecuador may experience the greatest increase in incidence in both sexes by 2030 (2).

In addition, the widespread use of imaging has contributed to the earlier diagnosis of small renal masses (SRMs) (3). However, despite the increased detection and treatment of small tumors, the worldwide mortality rates have not been consistently reduced. This demonstrates the need for reassessment of this cancer (4).

Overall, tumor-related factors, such as pathological stage, tumor size, nuclear grade, and histological subtype, had the most important independent prognostic impact (5). Nevertheless, grouping these data into clinical, demographic, and biomolecular parameters can lead to a better analysis.

Rationale and knowledge gap

Increasing efforts to study prognostic factors related to RCC may shorten the regional discrepancies, particularly in the scenario of scarce literature in LA, in comparison to Europe or North America (6,7).

The evaluation of RCC prognosis allows a greater capacity to anticipate outcomes, in addition to a better understanding of tumor biology and the orientation of the proposed treatment.

Health equity is directly related to understanding regional disparities and the health determinants of a region, such as differences in personal, social, economic, and environmental factors of individuals or populations (8).

Objective

Considering the progress of publications about RCC in LA, we provide a review of the main prognostic factors described in different stages of the disease. We present this article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-22-110/rc).

Methods

The PubMed database was used to identify studies on this theme, particularly those from LA. Studies by the Latin American Renal Cancer Group (LARCG) and the Latin American Cooperative Oncology Group (LACOG) were included. TCM and DA selected the main articles used in this study. *Table 1* presents a summary of the search strategy.

Prognostic factors

Clinical and demographic factors

LA represents a large geographic area, with most of the population living in developing countries (9). Over time, a singular ethnic group has mixed, consisting of indigenous natives and European, Asian, and African immigrants, which could be associated with unique predictors.

Age and male sex are well established predictors of malignancy. The highest incidence rates occur around the seventh decade of life and the median age of death is 72 years (10-13). Advanced age is also associated with worse cancer-specific mortality (14).

In LA, elderly people aged ≥60 years were associated with an almost three-fold increase in mortality rate compared to younger patients up to 40 years in a cohort of non-metastatic RCC patients (15).

Female sex has already been described as being related

Table 1 The search strategy summary

Items	Specification
Date of search	November 2022
Databases and other sources searched	PubMed
Search terms used	[("Kidney Cancer" OR "Renal Cell Carcinoma") AND ("Prognostic factors" OR Predictors)] OR [("Kidney Cancer" OR "Renal Cell Carcinoma") AND "Latin America"]
Timeframe	2000–2022
Inclusion criteria	Included papers in English, Spanish or Portuguese
Selection process	TC Mourão and D Abreu selected the papers
Additional consideration	Papers from the LARCG and from the LACOG were considered

LARCG, Latin American Renal Cancer Group; LACOG, Latin American Cooperative Oncology Group.

to a 19% reduction in the mortality rate from cancer compared to the male sex. However, this difference was not observed in women aged >59 years (16).

Regarding the clinical prognostic factors, smoking has been associated to high-grade tumors. Some studies have shown that risk progresses directly to tobacco load and the duration of the addiction (17). In a LA series, former smokers had lower overall survival (OS) and cancer-specific survival (CSS) rates, but the difference was not statistically significant (15). Further studies are required to clarify this issue.

The presence of systemic symptoms, such as weight loss, fever, anorexia, night sweats, enlarged cervical lymph nodes, bilateral varicoceles, lower limb edema, or hepatosplenomegaly, are associated with advanced disease. Another point is the diagnosis of paraneoplastic syndrome, which occurs with anemia, elevated erythrocyte sedimentation rate, coagulopathies, high alkaline phosphatase levels, hypercalcemia, polycythemia, or arterial hypertension (18). These signs and symptoms can affect both the OS and CSS (15).

The Karnofsky and Eastern Cooperative Oncology Group (ECOG) performance scores are largely used in oncological patients. The prognostic value of these classification systems has been demonstrated for decades in RCC (19,20). Similarly, the American Society of Anesthesiologists (ASA) classification system was described as an independent predictor of OS and CSS in studies from LA. The patients classified as ASA ≥3 have a higher risk of disease progression or cancer death, besides of more chance of surgical complications (21,22). In a study from the LARCG comprising 5,670 non-metastatic clear cell RCC (ccRCC) patients, ASA classification ≥3 increased the risk of death by 48% in a multivariate analysis (15). Another study analyzed 530 patients with *de novo* metastases. Most patients have previously undergone cytoreductive nephrectomy. The authors proposed stratification into risk groups for 5-year OS based on ASA classification, presence of perirenal fat invasion, and the number of metastatic sites (23).

At this point, the geographic region itself did not influence survival outcomes in a pooled analysis of patients with metastatic RCC who were treated in selected clinical trials. In that study, OS in LA was similar to that in other world regions (8).

Anatomical and histological factors

Most histological subtypes are ccRCC, followed by papillary RCC. Both originated from the proximal convoluted tubules. The third most frequent subtype is chromophobe RCC, which occurs more distally in the nephron.

Most tumors are solitary lesions, and bilateral involvement can occur in 2–4 % of sporadic neoplasms. In addition, multicentricity is found in approximately 10–20% of patients, particularly in the papillary subtype (5,24).

Regarding tumor size, up to 30% of SRM have benign histology. If the masses are less than 2 cm in size, up to 40% are benign. Furthermore, malignant SRM often demonstrate indolent behavior (25-28). A retrospective series from LA studied SRM in more than 1,500 patients. It was described that the extracapsular extension, the bilaterality, and patients with ASA ≥3 increase the risk of recurrence in this setting (9).

The nuclear features are independent prognostic factors for ccRCC and papillary subtypes (29-31). Currently, nuclear grade classification is described by the International

Society of Urological Pathology (ISUP) and the World Health Organization based on nucleolar characteristics, presence of pleomorphisms, and sarcomatoid or rhabdoid features (32). In addition, tumor size and nuclear grade were not associated with worse prognosis in chromophobe RCC patients than in ccRCC patients (33). Variant histologies showing sarcomatoid or rhabdoid differentiation show worse CSS (34).

The identification of an infiltrative growth pattern is implied in the prognosis of the disease and commonly requires the differential diagnosis of urothelial carcinoma, lymphomas, or even non-neoplastic pathologies. Sarcomatoid variants or collecting duct carcinoma are exceptions to this infiltrative pattern. In contrast, cystic lesions are associated with better prognosis than solid tumors (5).

Several histopathological features have been described in RCC patients. Therefore, renal capsule, renal sinus, or collecting system invasion is found in up to 20% of cases. These aspects represent the aggressive behavior of the neoplasia. A notable aspect is the predilection of RCC for venous system involvement in approximately 10% of cases (35). Venous tumoral thrombi may be present in the renal vein or extend to the vena cava or even the right atrium. The commitment of the wall of the vena cava is associated with worse prognosis and integrates a part of the tumor-node-metastasis (TNM) classification system (35-37).

Although patients with perirenal fat infiltration or renal sinus fat invasion are grouped at the same tumor stage (pT3a), evidence suggests prognostic differences in these cases. In a previous study, the combination of these two pathological characteristics resulted in an unfavorable oncological outcome and a higher association with metastasis. The 5-year CSS rates were 64.6% and 63.3% in the groups with only perirenal fat infiltration and renal sinus infiltration, respectively. However, considering the combination of these variables, the rate was only 31% (38).

These findings were also observed in the LARCG group, where the concomitant involvement of the perirenal fat and renal sinus led to worse CSS [hazard ratio (HR) =4.5] and a higher risk of local or systemic recurrence (HR =8.08 and HR =2.42, respectively) (39).

Another LA study evaluated 220 patients who were treated between 1992 and 2009. The presence of perirenal fat invasion concomitant with renal vein invasion presented almost triple the risk of cancer death and more than twice the risk of progression compared with patients with only one of these factors (40).

Regarding tumor surgical margins, more discussions have appeared after the dissemination of nephron-sparing surgeries. Indeed, several reports have revealed no association between recurrence and salvage treatments, particularly for T1 lesions (41,42). Notwithstanding, there is significant concern in high-risk patients, such as those with pT2 stage or high nuclear grade (43).

An analysis from a large multicenter database in eight countries from LA and Spain described the prognostic impact of other histopathological factors, such as the presence of tumor necrosis (10-year OS, 54.4%; 10-year CSS, 67.9%), microvascular invasion (10-year OS, 56.6%; 10-year CSS, 65.9%), and renal pelvis infiltration, venous invasion, and adrenal gland involvement. In this study, the positive surgical margins showed a decrease of approximately 10% in the 10-year CSS, but it did not persist as an independent predictor in multivariate analysis (15).

Among these metastatic patients, Abreu *et al.* [2020] showed in a study of 530 metastatic RCC cases that the presence of spinal bone metastasis predicted shorter OS than patients with non-spinal bone metastasis. In this population, ASA 3–4, non-clear cell histology, and age were independent predictors of death (44).

Molecular factors

The ability to identify genes or proteins associated with more or less aggressive cancers would lead to a better capacity to assess prognosis as well as more individualized treatment. Several potential molecular markers that impact oncological outcomes have been suggested. However, the routine use of these markers has not been applied in current clinical practice. Some breakthrough findings in ccRCC from The Cancer Genome Atlas (TCGA) research network include the identification of alterations in genes related to von Hippel-Lindau (VHL) proteins, such as *PBRM1*, *BAP1*, and *SETD2* (5).

It has already been suggested that certain alterations in the VHL gene (locus 3p25-p26) could be related to some clinical variables, such as loss of heterozygosity and association with nuclear grade, lymph node involvement, or tumoral necrosis. However, it was not possible to determine the prognostic effects of these alterations (45).

Patard *et al.* analyzed the role of VHL gene mutations and immunohistochemical expression of type IX carbonic anhydrase (CA-IX) in 100 patients who underwent surgical treatment. In that study, the absence of VHL mutations

and low CA-IX expression was associated with advanced disease and the presence of metastases. On multivariate analysis, only CA-IX expression was identified as an independent prognostic factor (46). Another study evaluated the mutational status of VHL and its clinical impact in patients with sporadic ccRCC. In that study, VHL protein expression was present in 80% of cases and was not associated with survival. Only nonsense-type mutations (5% of cases) appear to be associated with a worse prognosis (47).

CA-IX appears to play a role in regulating intra- and extracellular pH during periods of hypoxia in tumor cells. It has been reported that about 94% of ccRCC cells stain positively for CA-IX. Low expression of this marker is associated with poor survival rates (48-50). In patients with low CA-IX expression, concomitant high expression of Ki67 was an independent predictor of worse survival (48). As a counterpoint, immunohistochemical analysis of the MIB-1/Ki-67 marker was performed in patients with localized ccRCC. There is no association between recurrence and cancer-related mortality (51).

Among other frequently identified gene alterations, it is possible to cite mutations in *PBRM1* (up to 41%), *SETD2* (up to 12%), and *BAP1* (up to 11% of cases), among others. These three genes are located on the short arm of chromosome 3 (52).

The BAF180 protein, encoded by the *PBRM1* gene, is a subunit of the switch defective/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex. This promotes the mobilization of chromatin histones. This complex has the characteristics of a tumor suppressor gene, and mutations in its subunits are associated with other cancers. Immunohistochemical expression of *PBRM1* in neoplastic renal tissue was previously analyzed, showing that the absence of expression of this marker was associated with worse tumor stage, in addition to worse CSS, and recurrence-free survival (RFS) (53). Other authors have reported similar results associated with tumor aggressiveness and the absence of expression of this gene (54,55).

BAP1 encodes BRCA-1-associated protein-1, which acts as a deubiquitinating enzyme and regulates multiple cellular pathways related to carcinogenesis. In two recent studies, da Costa *et al.* reported that the loss of *BAP1* immunohistochemical expression in metastatic tumor tissue resulted in worse survival rates. Furthermore, even tumors in earlier stages, which had a concomitant loss of *PBRM1* and *BAP1* expression, presented a higher risk of recurrence and cancer death (56,57).

Similarly, the expression of *SETD2* was analyzed in 662 ccRCC cases. It has been suggested to be an independent predictor of 10-year CSS and OS in these patients, with over 60% higher risk (58). Its role as a prognostic biomarker has also been suggested in metastatic disease, particularly in the ccRCC subtype, in patients in the intermediate-risk group, according to the International Metastatic RCC Database Consortium (IMDC) criteria (59).

Other genes are also implicated in the prognosis of RCC, such as the chromatin remodeling genes *EZH2* and *KDM5C*, in addition to the DNA-repair genes *MET*, *TERT*, *NF2*, *SMARCB1*, *TFE3*, and genes related to the mTOR signaling pathway, such as the *PTEN* tumor suppressor gene, and the *MTOR* gene itself (52,60,61). This research field is vast, and contradictory results are often common. *PTEN* gene expression was analyzed in 53 cases. Gene deletions were observed in 40% of the samples. There is no evidence of a relationship between poor survival rates and poor prognostic factors (62).

Mutations in *TP53* tumor suppressor genes have been associated with several cancers. In an analysis of TCGA data, *TP53* mutations were associated with survival in ccRCC and papillary and chromophobe subtypes (63). Morshaeuser *et al.* performed external validation of a panel with multiple molecular markers. They showed a cut-off point of 20% for p53 protein expression with an impact on disease progression and cancer-specific mortality (64). Overexpression of p53 has also been associated with poor prognosis in other studies (65-67).

In a study carried out in LA, CD44 and CD133 stem cell markers were separately evaluated by immunohistochemical expression in a population of ccRCC patients who underwent surgical treatment. Low CD133 expression is an independent predictor of CSS and progression-free survival. In contrast, overexpression of CD44 glycoprotein was associated only with stage and nuclear grade, but it did not affect survival (68,69). This is still a debatable issue, and a previous meta-analysis showed an association between the overexpression of CD44 and worse OS and CSS. CD133 expression is a protective factor against CSS (70).

A study conducted in Brazil analyzed a series of markers using immunohistochemical expression. Among them, extracellular matrix metalloproteinases, a set of enzymes that may be related to metastasis mechanisms, are associated with poor prognosis. The nitric oxide synthases, which mediate the production of nitric oxide, are associated with several tumors. In this study, nitric oxide synthase 3 (NOS-3) was associated with worse OS and larger tumor size (71).

The cellular apoptosis pathway requires the activation

of initiator and effector caspases. The lack of expression of these proteins can result in impaired signaling that leads to cell death, allowing the uncontrolled growth of neoplastic cells. Vilella-Arias *et al.* investigated the role of loss of expression of caspase 7, an effector caspase, in the aggressiveness of renal tumors. Tumor tissues show lower expression of this marker, and are associated with worse CSS and a higher rate of recurrence (72).

Blockade of the immune checkpoint has gained great prominence in the treatment of systemic diseases, as well as in the potential adjuvant role of agents such as anti-programmed cell death protein 1 (PD-1), anti-programmed cell death ligand 1 (PD-L1), or anti-CTLA-4. The prognostic value of PD-1 and PD-L1 expression was evaluated in a study of 1,017 (738 available) cases. The positivity of these markers was associated with higher tumor stage, necrosis, and lymphovascular invasion. In addition, PD-L1 expression was an independent predictor of worse RFS, which may represent a tool for better stratification of patients undergoing adjuvant therapy (73).

Among the cell cycle regulators involved in cancer development, cyclin D1 is one of the most prevalent, and its overexpression has been observed in several tumors. In RCC, a Brazilian study evaluated 109 tumor samples and demonstrated that low expression (up to 30% of positive cells) was associated with worse clinical outcomes and poor prognostic characteristics such as high nuclear grade, large tumor size, necrosis, and sarcomatoid pattern (74).

Kovacs *et al.* analyzed the role of β-catenin, a protein involved in several cell signaling pathways, playing a role mainly as a transcription factor and a protein related to cell adhesion. The authors reported that the expression of this marker was associated with a four-fold greater risk of death from cancer (75).

Finally, another line of research considered the kidney to be an endocrine organ. Thus, the study of proteins produced in the renal cortex can aid in a better understanding of renal cancer carcinogenesis.

Ferreira *et al.* [2017] and de Almeida E Paula *et al.* [2019] have contributed to the understanding of possible biomarkers involved in RCC. First, it was shown that the lack of immunohistochemical expression of erythropoietin was an independent predictive factor for the prognosis of cancer. Second, the absence of intratumoral renin expression was associated with high-grade tumors and venous vascular invasion and was found to be an unfavorable prognostic factor for disease-free survival in multivariate analysis (76,77).

Prognostic models

Multifactorial mathematical models have been developed in recent years to serve as prognostic tools and stratify patients into risk categories.

Abnormal laboratory values associated with Karnofsky performance status led to the development of the main prognostic models of advanced RCC, the Memorial Sloan Kettering Cancer Center (MSKCC), and the IMDC (78-81).

In the setting of non-metastatic disease, the main algorithms for use include the Mayo Clinic SSIGN (Stage, Size, Grade, and Necrosis) score, MSKCC Kattan nomogram, and University of California at Los Angeles (UCLA) integrated staging system, called the UCLA Integrated Staging System (UISS) for renal cell carcinoma (82-84). TNM stage is present in these nomograms, in addition to variables such as nuclear grade, tumor size, presence of signs or symptoms, performance status, and presence of tumor necrosis.

Recently, a prognostic score for disease-free survival called GRANT (Grade, Age, Nodes, and Tumor) was validated using a large population of patients with RCC from the ASSURE clinical trial involving adjuvant therapy (85).

The UISS score is related to 5-year disease-free survival. This score differs according to the staging of the disease, with one existing for localized disease and another for metastatic disease. In localized disease, the T stage, Fuhrman nuclear grade, and ECOG performance status were evaluated. In the metastatic scenario, the N and M stages were evaluated. According to this score, non-metastatic patients had 5-year OS and CSS rates of 83.8% and 91.1% in the low-risk group, 71.9% and 80.4% in the intermediate-risk group, and 44% and 54.7% in the high-risk group, respectively (86).

The Kattan nomogram was developed to predict RFS in patients who underwent surgical treatment. Among the variables, 1997 TNM pathological staging, histological subtype, symptomatology, and tumor size were used (86).

The SSIGN score was originally proposed to predict CSS in surgically treated ccRCC patients. Ten categories were described with different 10-year CSS rates. Subsequently, the algorithm was updated to estimate disease-free survival in patients with non-metastatic RCC. The authors proposed stratification into the low-risk group (scores 0–2), intermediate-risk group (scores 3–5), and high-risk of progression (scores ≥6) (86). More recently, a retrospective analysis demonstrated that this tool remains

Table 2 Model of risk group stratification in *de novo* metastatic patients from Latin America (risk factors: ASA 3–4; perirenal fat invasion; metastases ≥2 organs)

Risk group stratification	No. risk factors	Median OS (months)	HR (95% CI)
Favorable-risk group	0	NR	–
Intermediate-risk group	1	33	2.04 (1.14–3.65); P=0.016
Poor risk group	2–3	14	3.58 (2.02–6,34); P<0.0001

Adapted from Abreu *et al.* [2021] (23). Permission is obtained from the publisher. ASA, American Society of Anesthesiologists; OS, overall survival; HR, hazard ratio; CI, confidence interval; NR, not reached.

useful in patients with a longer follow-up time (>20 years) and maintains its predictive capacity in a contemporary series of patients who have undergone partial or radical nephrectomy (87).

In LA, a report from the LARCG created a risk group stratification in *de novo* metastatic patients according to the following variables associated with OS in the multivariate analysis: perirenal fat invasion, ≥2 metastatic organ sites, and ASA classification 3–4 at the time of surgery (*Table 2*) (23).

In terms of the strengths and limitations of this review, we were able to discuss the main topics around prognostic factors in RCC, not only in LA but also in classical international literature, which is essential to this theme. We could cite a vast literature from LA regarding several potential biomolecular factors in localized or metastatic RCC. Despite these strengths, this study had some important limitations. Most studies involving prognostic factors in LA are retrospective analyses. In studies on potential biomarkers, most of them used tissue microarray preparations and immunohistochemical assessments. Some technical issues are important, such as possible inadequate fixation, potential loss of antigenicity over time, and tumor heterogeneity in different areas.

Conclusions

Anatomical and histological prognostic factors of RCC have been widely studied for decades. In recent years, biomolecular factors have attracted considerable attention. LA centers played an important role in these research lines. To maintain advancements in the different settings of RCC, larger engagement in clinical trials and prospective studies must be encouraged.

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Wong MCS, Goggins WB, Yip BHK, et al. Incidence and mortality of kidney cancer: temporal patterns and global trends in 39 countries. Sci Rep 2017;7:15698.
3. Nguyen MM, Gill IS, Ellison LM. The evolving presentation of renal carcinoma in the United States: trends from the Surveillance, Epidemiology, and End Results program. J Urol 2006;176:2397-400; discussion 2400.
4. Hollingsworth JM, Miller DC, Daignault S, et al. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst 2006;98:1331-4.
5. Campbell SC, Lane BR, Pierorazio PM. Malignant renal tumors. In: Partin A, Dmochowski RR, Kavoussi L, et al. editors. Campbell-Walsh-Wein Urology. 12th ed. Philadelphia: Elsevier; 2021:2133-84.
6. Grandez-Urbina JA, Arias-Nolazco R. Renal cell carcinoma in Latin America: Do we know the relationship between demographic changes and the impact on our population? Actas Urol Esp 2017;41:280.
7. Zequi SC, Clavijo DA. The creation, development and diffusion of the LARCG latin american renal cancer group. Int Braz J Urol 2017;43:3-6.
8. Fay AP, McKay RR, Lin X, et al. Impact of Geographic Regions on Overall Survival in Patients With Metastatic Renal Cell Carcinoma: Results From an International Clinical Trials Database. J Glob Oncol 2018;4:1-14.
9. 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 2020;20:85.
10. Snyder ME, Bach A, Kattan MW, et al. Incidence of benign lesions for clinically localized renal masses smaller than 7 cm in radiological diameter: influence of sex. J Urol 2006;176:2391-5; discussion 2395-6.
11. Capitanio U, Bensalah K, Bex A, et al. Epidemiology of Renal Cell Carcinoma. Eur Urol 2019;75:74-84.
12. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2018. Bethesda, MD: National Cancer Institute; 2021.
13. Pierorazio PM, Patel HD, Johnson MH, et al. Distinguishing malignant and benign renal masses with composite models and nomograms: A systematic review and meta-analysis of clinically localized renal masses suspicious for malignancy. Cancer 2016;122:3267-76.
14. Bandini M, Marchioni M, Pompe RS, et al. The effect of age on cancer-specific mortality in patients with small renal masses: A population-based analysis. Can Urol Assoc J 2018;12:E325-30.
15. Zequi SC, Mourão TC, de Oliveira MM, et al. Predictors of Survival Outcomes in Non-Metastatic Renal Cell Carcinoma in Latin America and Spain: A Multicentric Analysis. Kidney Cancer 2019;3:253-61.
16. Rampersaud EN, Klatte T, Bass G, et al. The effect of gender and age on kidney cancer survival: younger age is an independent prognostic factor in women with renal cell carcinoma. Urol Oncol 2014;32:30.e9-13.
17. Lotan Y, Karam JA, Shariat SF, et al. Renal-cell carcinoma risk estimates based on participants in the prostate, lung, colorectal, and ovarian cancer screening trial and national lung screening trial. Urol Oncol 2016;34:167.e9-16.
18. Eble JN, Sauter G, Epstein JI, et al. World Health Organization classification of tumours: Pathology and genetics of tumours of the urinary system and male genital organs. Eble JN, Sauter G, Epstein JI, et al. editors. Lyon, France: IARC Press; 2004.
19. Patard JJ, Kim HL, Lam JS, et al. Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. J Clin Oncol 2004;22:3316-22.
20. Shuch B, La Rochelle JC, Wu J, et al. Performance status and cytoreductive nephrectomy: redefining management in patients with poor performance. Cancer 2008;113:1324-31.
21. de Cássio Zequi S, de Campos EC, 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;84:67-72.
22. Ferreira DB, Zequi SC, da Costa WH, et al. Use of the American Society of Anesthesiologists Classification as an Additional Planning Tool for Renal Cell Carcinoma Assessment. J Cancer Ther 2013;4:7-14.
23. Abreu D, Carvalhal G, Gueglio G, et al. Prognostic Factors in De Novo Metastatic Renal Cell Carcinoma: A Report From the Latin American Renal Cancer Group. JCO Glob Oncol 2021;7:671-85.
24. Krambeck A, Iwaszko M, Leibovich B, et al. Long-term outcome of multiple ipsilateral renal tumours found at the time of planned nephron-sparing surgery. BJU Int 2008;101:1375-9.
25. Frank I, Blute ML, Cheville JC, et al. Solid renal tumors: an analysis of pathological features related to tumor size. J Urol 2003;170:2217-20.
26. Kutikov A, Fossett LK, Ramchandani P, et al. Incidence of benign pathologic findings at partial nephrectomy for solitary renal mass presumed to be renal cell carcinoma on preoperative imaging. Urology 2006;68:737-40.
27. Umbreit EC, Shimko MS, Childs MA, et al. Metastatic potential of a renal mass according to original tumour size at presentation. BJU Int 2012;109:190-4; discussion 194.
28. Johnson DC, Vukina J, Smith AB, et al. Preoperatively misclassified, surgically removed benign renal masses: a systematic review of surgical series and United States population level burden estimate. J Urol 2015;193:30-5.
29. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982;6:655-63.
30. Klatte T, Rossi SH, Stewart GD. Prognostic factors and prognostic models for renal cell carcinoma: a literature review. World J Urol 2018;36:1943-52.
31. Delahunt B, Eble JN, Samaratunga H, et al. Staging of renal cell carcinoma: current progress and potential advances. Pathology 2021;53:120-8.
32. Delahunt B, Cheville JC, Martignoni G, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol 2013;37:1490-504.
33. Steffens S, Roos FC, Janssen M, et al. Clinical behavior of chromophobe renal cell carcinoma is less aggressive than that of clear cell renal cell carcinoma, independent of Fuhrman grade or tumor size. Virchows Arch 2014;465:439-44.
34. Deuker M, Stolzenbach F, Rosiello G, et al. Renal Cell Carcinoma: Comparison between Variant Histology and Clear Cell Carcinoma across All Stages and Treatment Modalities. J Urol 2020;204:671-6.
35. Schefft P, Novick AC, Straffon RA, et al. Surgery for renal cell carcinoma extending into the inferior vena cava. J Urol 1978;120:28-31.
36. Zini L, Destrieux-Garnier L, Leroy X, et al. Renal vein ostium wall invasion of renal cell carcinoma with an inferior vena cava tumor thrombus: prediction by renal and vena caval vein diameters and prognostic significance. J Urol 2008;179:450-4; discussion 454.
37. Haddad AQ, Wood CG, Abel EJ, et al. Oncologic outcomes following surgical resection of renal cell carcinoma with inferior vena caval thrombus extending above the hepatic veins: a contemporary multicenter cohort. J Urol 2014;192:1050-6.
38. Bedke J, Buse S, Pritsch M, et al. Perinephric and renal sinus fat infiltration in pT3a renal cell carcinoma: possible prognostic differences. BJU Int 2009;103:1349-54.
39. García Marchiñena P, Tobia I, Abreu D, et al. Valor pronóstico de la invasión de grasa perirrenal y/o del seno en pacientes con carcinoma de células renales pT3a: estudio de cohorte multicéntrico. Grupo LARCG. Actas Urológicas Españolas 2019;43:495-502.
40. da Costa WH, Moniz RR, da Cunha IW, et al. Impact of renal vein invasion and fat invasion in pT3a renal cell carcinoma. BJU Int 2012;109:544-8.
41. Lam JS, Bergman J, Breda A, et al. Importance of surgical margins in the management of renal cell carcinoma. Nat Clin Pract Urol 2008;5:308-17.
42. Kang HW, Lee SK, Kim WT, et al. Surgical margin does not influence recurrence rate in pT1 clear cell renal cell carcinoma after partial nephrectomy: A multicenter study. J Surg Oncol 2016;114:70-4.
43. Shah PH, Moreira DM, Okhunov Z, et al. Positive Surgical Margins Increase Risk of Recurrence after Partial Nephrectomy for High Risk Renal Tumors. J Urol 2016;196:327-34.
44. Abreu D, Angeli Gazola A, de Souza ABA, et al. 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). J Cancer Sci Clin Ther 2020;4:526-37.
45. Young AC, Craven RA, Cohen D, et al. Analysis of VHL Gene Alterations and their Relationship to Clinical Parameters in Sporadic Conventional Renal Cell Carcinoma. Clin Cancer Res 2009;15:7582-92.
46. Patard JJ, Fergelot P, Karakiewicz PI, et al. Low CAIX expression and absence of VHL gene mutation

are associated with tumor aggressiveness and poor survival of clear cell renal cell carcinoma. Int J Cancer 2008;123:395-400.
47. Alves MR, Carneiro FC, Lavorato-Rocha AM, et al. Mutational status of VHL gene and its clinical importance in renal clear cell carcinoma. Virchows Arch 2014;465:321-30.
48. Bui MH, Visapaa H, Seligson D, et al. Prognostic value of carbonic anhydrase IX and KI67 as predictors of survival for renal clear cell carcinoma. J Urol 2004;171:2461-6.
49. Atkins M, Regan M, McDermott D, et al. Carbonic anhydrase IX expression predicts outcome of interleukin 2 therapy for renal cancer. Clin Cancer Res 2005;11:3714-21.
50. Downs TM, Schultzel M, Shi H, et al. Renal cell carcinoma: risk assessment and prognostic factors for newly diagnosed patients. Crit Rev Oncol Hematol 2009;70:59-70.
51. Zequi SC. Correlação entre os fatores clínicos e anatomopatológicos associados aos índices de proliferação celular como prognósticos em portadores de câncer do rim tratados por cirurgia [dissertation]. São Paulo: Fundação Antônio Prudente, A.C.Camargo Cancer Center; 2000.
52. Morris MR, Latif F. The epigenetic landscape of renal cancer. Nat Rev Nephrol 2017;13:47-60.
53. da Costa WH, Rezende M, Carneiro FC, et al. Polybromo-1 (PBRM1), a SWI/SNF complex subunit is a prognostic marker in clear cell renal cell carcinoma. BJU Int 2014;113:E157-63.
54. Pawłowski R, Mühl SM, Sulser T, et al. Loss of PBRM1 expression is associated with renal cell carcinoma progression. Int J Cancer 2013;132:E11-7.
55. Joseph RW, Kapur P, Serie DJ, et al. Clear Cell Renal Cell Carcinoma Subtypes Identified by BAP1 and PBRM1 Expression. J Urol 2016;195:180-7.
56. da Costa WH, da Cunha IW, Fares AF, et al. Prognostic impact of concomitant loss of PBRM1 and BAP1 protein expression in early stages of clear cell renal cell carcinoma. Urol Oncol 2018;36:243.e1-8.
57. da Costa WH, Fares AF, Bezerra SM, et al. Loss of BAP1 expression in metastatic tumor tissue is an event of poor prognosis in patients with metastatic clear cell renal cell carcinoma. Urol Oncol 2019;37:78-85.
58. Santos VE, da Costa WH, Bezerra SM, et al. Prognostic Impact of Loss of SETD2 in Clear Cell Renal Cell Carcinoma. Clin Genitourin Cancer 2021;19:339-45.
59. Wang J, Liu L, Qu Y, et al. Prognostic Value of SETD2 Expression in Patients with Metastatic Renal Cell Carcinoma Treated with Tyrosine Kinase Inhibitors. J Urol 2016;196:1363-70.
60. Mitchell TJ, Rossi SH, Klatte T, et al. Genomics and clinical correlates of renal cell carcinoma. World J Urol 2018;36:1899-911.
61. Dizman N, Philip EJ, Pal SK. Genomic profiling in renal cell carcinoma. Nat Rev Nephrol 2020;16:435-51.
62. de Campos EC, da Fonseca FP, Zequ Sde C, et al. Analysis of PTEN gene by fluorescent in situ hybridization in renal cell carcinoma. Rev Col Bras Cir 2013;40:471-5.
63. Li VD, Li KH, Li JT. TP53 mutations as potential prognostic markers for specific cancers: analysis of data from The Cancer Genome Atlas and the International Agency for Research on Cancer TP53 Database. J Cancer Res Clin Oncol 2019;145:625-36.
64. Morshaeuser L, May M, Burger M, et al. p53-expression in patients with renal cell carcinoma correlates with a higher probability of disease progression and increased cancer-specific mortality after surgery but does not enhance the predictive accuracy of robust outcome models. Urol Oncol 2018;36:94.e15-21.
65. Girgin C, Tarhan H, Hekimgil M, et al. P53 mutations and other prognostic factors of renal cell carcinoma. Urol Int 2001;66:78-83.
66. Noon AP, Vlatković N, Polański R, et al. p53 and MDM2 in renal cell carcinoma. Cancer 2010;116:780-90.
67. Wang Z, Peng S, Jiang N, et al. Prognostic and clinicopathological value of p53 expression in renal cell carcinoma: a meta-analysis. Oncotarget 2017;8:102361-70.
68. Costa WH, Rocha RM, Cunha IW, et al. Immunohistochemical expression of CD44s in renal cell carcinoma lacks independent prognostic significance. Int Braz J Urol 2012;38:456-65.
69. Costa WH, Rocha RM, Cunha IW, et al. CD133 immunohistochemical expression predicts progression and cancer-related death in renal cell carcinoma. World J Urol 2012;30:553-8.
70. Cheng B, Yang G, Jiang R, et al. Cancer stem cell markers predict a poor prognosis in renal cell carcinoma: a meta-analysis. Oncotarget 2016;7:65862-75.
71. Cássio Zequi SC, Fregnani JH, Favaretto RL, et al. The impact of immunohistochemical expression of nitric oxide synthases on clinical and pathological features of renal cell carcinoma. World J Urol 2013;31:1197-203.
72. Vilella-Arias SA, Rocha RM, da Costa WH, et al. Loss of caspase 7 expression is associated with poor prognosis in renal cell carcinoma clear cell subtype. Urology 2013;82:974.e1-7.
73. Chipollini J, da Costa WH, Werneck da Cunha I, et

al. Prognostic value of PD-L1 expression for surgically treated localized renal cell carcinoma: implications for risk stratification and adjuvant therapies. Ther Adv Urol 2019;11:1756287219882600.
74. Lima MS, Pereira RA, Costa RS, et al. The prognostic value of cyclin D1 in renal cell carcinoma. Int Urol Nephrol 2014;46:905-13.
75. Kovacs G, Billfeldt NK, Farkas N, et al. Cytoplasmic expression of β-catenin is an independent predictor of progression of conventional renal cell carcinoma: a simple immunostaining score. Histopathology 2017;70:273-80.
76. Ferreira DB, da Costa WH, Clavijo DA, et al. Tissue Expression of Erythropoietin Predicts Survival Rates in Clear Cell Renal Cell Carcinoma. Kidney Cancer 2017;1:143-9.
77. de Almeida E Paula F, Bezerra SM, da Cunha IW, et al. Immunohistochemical expression of renin is a prognostic factor for recurrence in nonmetastatic renal cell carcinoma. Urol Oncol 2019;37:947-54.
78. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530-40.
79. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20:289-96.
80. Goebell PJ, Ivanyi P, Bedke J, et al. Consensus paper: current state of first- and second-line therapy in advanced clear-cell renal cell carcinoma. Future Oncol 2020;16:2307-28.
81. 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 2009;27:5794-9.
82. Kattan MW, Reuter V, Motzer RJ, et al. A postoperative prognostic nomogram for renal cell carcinoma. J Urol 2001;166:63-7.
83. Frank I, Blute ML, Cheville JC, et al. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol 2002;168:2395-400.
84. Zisman A, Pantuck AJ, Wieder J, et al. Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. J Clin Oncol 2002;20:4559-66.
85. Buti S, Puligandla M, Bersanelli M, et al. Validation of a new prognostic model to easily predict outcome in renal cell carcinoma: the GRANT score applied to the ASSURE trial population. Ann Oncol 2017;28:2747-53.
86. Galfano A, Novara G, Iafrate M, et al. Mathematical models for prognostic prediction in patients with renal cell carcinoma. Urol Int 2008;80:113-23.
87. Parker WP, Cheville JC, Frank I, et al. Application of the Stage, Size, Grade, and Necrosis (SSIGN) Score for Clear Cell Renal Cell Carcinoma in Contemporary Patients. Eur Urol 2017;71:665-73.

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