

Risk stratification and prognostication of renal cell carcinoma

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Abstract

Objectives To review the most recent data on prognostic factors and describe the characteristics and prognostic accuracy of the most important prognostic systems available to predict the risk of recurrence, progression, and mortality in patients with renal cell carcinoma (RCC).

Methods The study was based on a non-systematic review of literature.

Results Clinical (performance status, and mode of presentation), anatomical (size and extension of the primary tumor, lymph node involvement, and distant metastasis), and histological factors (histological subtypes, nuclear grade, and tumor necrosis) are the most largely evaluated prognostic factors in RCC. Valuable prognostic accuracy has been shown for several laboratory parameters (erythrocyte sedimentation rate, platelet count, serum calcium, hemoglobin, and lactate dehydrogenase levels) and a few genetical and molecular markers (CAIX, B7-H1, and B7-H4). A few integrating systems have been proposed and validated, integrating both clinical and pathological (UCLA Integrating Staging Systems, Kattan nomogram, and Sorbellini nomogram) or only pathological variables (SSIGN score).

Conclusions Several large and methodologically consistent studies have been published. The chance to integrate the data derived from each prognostic factor into prognostic algorithms and scores has allowed improving significantly the stratification of the prognosis of patients with RCC. The currently available prognostic systems can be further improved through the inclusion of molecular and genetic variables. Integrating prognostic systems should be used to design randomized controlled trials (RCTs), which will evaluate the efficacy of the new-targeted therapies in either neoadjuvant, adjuvant, or salvage treatments of patients with RCC.

Keywords Renal cell carcinoma · Cancer-specific survival · Prognostic factors · Nomogram · Scoring algorithms

Introduction

Stratification of the patients with renal cell carcinoma (RCC) into categories with different risk of local recurrence, progression, and survival has improved significantly the standard of preoperative patients' counseling, treatment planning, and definition of the most appropriate follow-up schedule, as well as design and interpretation of randomized controlled trials (RCTs) aiming at the evaluation of new medical and surgical therapies.

Several anatomical, clinical, histological, and molecular variables can predict the probabilities of recurrence, progression, and both overall and cancer-specific survival of the patients with RCC [1]. Since 2001, with the aim of improving the prognostic accuracy provided by every single available prognostic variable, several prognostic systems have been proposed, based on the integration of the main clinical and/or pathological features [2–7]. Although,

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to date, their use in everyday clinical practice is not really widespread, those integrating systems are extremely relevant in the field of clinical research, allowing more accurate selection of patients to be enrolled in the new RCTs and assessing the efficacy of new “targeted therapies” both in an adjuvant and metastatic setting [8, 9].

The purpose of the present review was to report the most recent data on the available prognostic factors as well as to describe the characteristics and prognostic accuracy of the most important prognostic systems available to predict the risk of recurrence, progression, and mortality of patients with RCC.

Anatomic prognostic factors

Anatomic prognostic factors include tumor size, extension of the primary tumor (T), loco-regional lymph node involvement (N), and presence of metastasis (M). Those data are clustered within the tumor nodes metastasis (TNM) classification, a dynamic staging system that has been progressively updated during the last decades to keep up with the new evidence from literature.

Cancer-specific survival probabilities ranged from 88 to 99% in pT1 RCCs, from 70.5 to 82% in those with pT2 cancers, from 10 to 60% in pT3 cases, and from 0 to 20% in pT4 cases. Moreover, in those patients with metastatic cancers disease-specific survival probabilities were in the range of 10–30% [10–16].

The evaluation of the most recent literature allows hypothesizing on further substantial revisions of the currently available TNM classification, with regards to localized (T1–2) and locally advanced (T3–4) RCC, as well as for those showing loco-regional lymph node involvement (N1–2) [17].

Although the current version of the TNM staging system can stratify appropriately the survival probabilities of patients with localized T1–2 RCC [14], several authors suggested different cut-off points of tumor size ranging from 4.5 to 5.5 cm to distinguish between T1 and T2 RCC [18]. A recently published European multicenter study, performed on 1,138 patients with a median follow-up duration as long as 87 months, proposed 5.5 cm as the most accurate cut-off point to stratify the cancer-related outcome of patients with localized RCC [19]. Other authors suggested the need to substratify the patients with T2 RCC into two different subgroups, according to the cut-off point of 10 cm [20] or, more recently, 11 cm [21].

Table 1 summarizes the most important proposals for revisions of the TNM staging systems of locally advanced RCC (Table 1) [15, 22, 23].

Urinary collecting system (UCS) involvement is not included in the current TNM staging system. Recent data from a large multicentric international series confirmed the absence of prognostic significance of urinary collecting system invasion, with 10-year cancer-specific survival rates of 70%, similar to those in T2 patients (72%) [24]. Further studies should confirm whether UCS involvement could influence the outcome of organ-confined tumors. At this time, this pathologic finding should not be considered in the new TNM staging system.

The presence of metastasis within loco-regional lymph nodes causes a significant worsening of the cancer-related outcome in patients with RCC [16]. Moreover, significant differences in the cancer-specific survival rates of patients with N1 and N2 have been reported [25, 26]. The presence of at least four lymph nodes involved by metastases or the presence of metastatic RCC in 60% of the retrieved nodes [26], as well as the occurrence of extra nodal tumor growth [27], is among the proposed pathological features to

Table 1 Proposals for reclassification of locally advanced renal cell carcinoma

Stage (T)	Current TNM [22]	Thompson et al. [23]	Ficarra et al. [15]
T3a	Perirenal or sinus fat invasion Ipsilateral adrenal invasion	Renal vein thrombosis	Perirenal fat invasion Renal vein thrombosis Subdiaphragmatic vena cava thrombosis
T3b	Renal vein thrombosis Subdiaphragmatic vena cava thrombosis	Perirenal fat invasion	Renal vein or subdiaphragmatic vena cava thrombosis + perirenal fat infiltration Ipsilateral adrenal invasion
T3c	Supradiaphragmatic vena cava thrombosis	Renal vein + fat invasion Subdiaphragmatic vena cava thrombus	–
T3d	–	Subdiaphragmatic vena cava invasion. + fat involvement Supradiaphragmatic vena cava thrombus	–
T4	Gerota's fascia invasion	Gerota's fascia invasion Ipsilateral adrenal involvement	Ipsilateral adrenal invasion + renal vein or subdiaphragmatic vena cava thrombosis Gerota's fascia invasion Supradiaphragmatic vena cava thrombosis

improve the prognostic stratification of the patients with lymph node involvement by RCC. Loco-regional lymph node dissection seems to play a role in improving cancer-specific survival of patients with clinically positive lymph nodes, in cases where distant metastases are present [28] or not [29].

Clinical prognostic factors

Among the clinical variables, patient's performance status and the mode of presentation of the tumor are the most largely evaluated.

ECOG and Karnofsky classifications are the most commonly applied systems to assign the performance status of patients with RCC. The prognostic role of the ECOG performance status was recently reconfirmed in a large multicenter multinational series of patients who had undergone nephrectomy for either localized or metastatic RCC [30, 31]. On the other hand, Karnofsky's performance status was largely used in clinical trials, which evaluated the efficacy of systemic therapies in patients with metastatic RCC. Specifically, Karnofsky's performance status was shown to be an independent predictor of survival for patients with metastatic RCC undergoing both first-line [4] and second-line [13] therapies.

With regards to the mode of presentation, patients with RCC can be distinguished into three categories with different prognosis. Asymptomatic patients (S1) have significantly more favorable cancer-specific survival rates, compared to those complaining of signs and symptoms of RCC (S2–3) [32]. Moreover, multicenter studies demonstrated that patients with the so-called local symptoms had significantly higher 5 and 10-year cancer specific survival rates, compared to those with systemic symptoms at the moment of the initial diagnosis of RCC [31, 33]. Although both ECOG performance status and presence of symptoms were independent predictors of cancer-specific survival, Karakiewicz et al. [31] recently showed that these two clinical variables did not increase substantially the prognostic accuracy of the mathematic models including the main pathological variables.

Preoperative erythrocyte sedimentation rate (ESR), platelet count, and calcium, hemoglobin, and lactate dehydrogenase (LDH) levels are the laboratory parameters, which have been more extensively studied as prognostic factors in patients with RCC.

Sengupta et al. [34] showed that elevated ESR was associated with unfavorable cancer-related outcome in patients with clear cell RCC, while its prognostic role failed to be confirmed in patients with papillary or chromophobe RCC.

With regards to platelet count, thrombocytosis, defined as at least a platelet count greater than $450,000/\text{mm}^3$, was

found to be associated with a worse prognosis in patients with both localized and metastatic RCC [35].

The prognostic role of high corrected serum calcium (>10 mg/dl), low serum hemoglobin (<13 g/dL for males and <11.5 g/dL for females), and high LDH (>1.5 times the upper limit of normal) was evaluated mainly in patients with metastatic RCC, undergoing first- or second-line systemic therapies [4, 13]. All the parameters were useful in predicting the survival of the patients treated with immuno- or chemo-immunotherapy as the first-line treatments [4]. Vice versa, high LDH was not an independent predictor of cancer-specific survival in patients with metastatic RCC undergoing second-line therapies [13].

Histological prognostic factors

Although several morphological, molecular, and genetic differences are evident among the different histological subtypes of RCC, the prognostic role of histotype is a very debatable topic. In 2003, Chevillet et al. [36] reported that the patients with clear cell RCC had significantly worse cancer-specific survival rates, compared to both papillary and chromophobe RCC, regardless of pathological stage and nuclear grade. A subsequent multicenter international study failed to reconfirm the independent predictive role of the histological subtype [37]. The main difference between the two studies has to be identified in the central review of the slide of nephrectomy specimens performed in a study at the Mayo Clinic, but not in the multicenter series. The lack of a pathological slide revision can cause a significant variation in the attribution of the histological subtype, mainly for the diagnoses made before 1997 [38], when the histological classifications of RCC was standardized for the first time [39]. Moreover, the fact that clear cell RCC is the most common histological subtype, as well as the one where cancer-related deaths are more common, may affect the ability of multivariate models to detect significant differences [25].

Fuhrman's classification is the system, which is most commonly used both in the US and Europe to assign nuclear grades in RCC. The system distinguishes four different grades, according to the size and morphology of nuclei, as well as the presence of nucleoli [40]. The independent predictive role of Fuhrman's grading systems was shown in several clinical studies. Moreover, literature data suggest that a three- or even a two-tiered system, clustering together the grades with similar cancer-related outcome, can be more effective in many series [41]. A recent multicenter study showed that different clustering of the four Fuhrman grades had limited effect on the prognostic accuracy [42]. Although the prognostic role of nuclear grades have been shown in a series of clear cell [36, 43], papillary [36, 44] and chromophobe RCC [36], recent data have

questioned the application of Fuhrman nuclear grades in patients with papillary [45] or chromophobe RCC [46].

Another important histological variable that may affect the prognosis of patients with RCC is the presence of tumor necrosis. The most common form of necrosis observed in RCC tumors is coagulative necrosis, characterized by homogeneous clusters and sheets of dead and degraded tumor cells that coalesce into an amorphous coagulum. This form of histologic coagulative necrosis was an independent predictor of malignant progression and death from cancer in clear cell carcinoma [5, 43]. However, the impact of histologic tumor necrosis on patient outcome varies by histologic subtype. Recently, Sengupta et al. reported that, although patients who have papillary RCC were more likely to have necrotic tumors compared with patients who have clear cell RCC or chromophobe RCC, the finding of necrosis in papillary RCC is not associated with death from disease. On the contrary, the finding of histologic tumor necrosis in clear cell RCC or chromophobe RCC is indicative of aggressive tumor behavior [47].

Data from literature indicate that the presence of sarcomatoid differentiation in RCC is associated with a median survival of less than 1 year [48]. In cases of RCC with sarcomatoid features, de Peralta-Venturina et al. reported 5 and 10-year survival rates of 22 and 13%, respectively. The Mayo Clinic team reported that cancer-specific survival rates at 2 years following surgery for patients who had clear cell, papillary, and chromophobe RCC with sarcomatoid differentiation were 30, 40, and 25%, respectively, compared with 84, 96, and 96%, respectively, for those patients who had RCC of the same histological subtype without sarcomatoid differentiation [25].

Molecular and genetic prognostic factors

The identification of molecular and genetic prognostic factors predictive of cancer-specific survival is the “holy grail” of translational research in RCC [49]. To date, a prognostic role has been suggested for hundreds of genes and proteins, including adhesion molecules (Cadherin-6, E-cadherin, MUC1/EMA, ICAM-1, VCAM-1, ELAM-1, KSA), molecules stimulating immune-response (HLA class I, interleukin-6, interleukin-8, IP-10, MIG, MIP-1 β , B7-H1, B7-H4, CD44), receptors of growth factors (VEGFR-3, TGF β R-II), hypoxia-inducible molecules (CAIX, CAXII, CXCR-4, HIF-1 α , VEGF, IGF-I), proliferation markers (Ki-67, PCNA, Ag-NORs), proteins regulating cell cycle (p53, bcl-2, PTEN, Cyclin A, Akt, p27) [50], and so on.

Carbonic anhydrase IX (CAIX) is among the most extensively studied prognostic factor. CA family catalyses the reversible conversion of carbon dioxide and water to carbonic acid, playing a role in the adaptation of tumors to

hypoxic conditions, regulating the pH of the intracellular and extracellular compartments. Although CAIX is limitedly expressed in the normal kidney, it is overexpressed in 95% of clear cell and 50% of papillary RCC. Specifically, in clear cell RCC where its prognostic role has been clearly shown, the loss of function of the VHL tumor suppressor gene by mutation or hypermethylation leads to an increase in hypoxia-inducible factor 1- α (HIF-1 α), which up-regulates CAIX expression [51]. Several authors demonstrated the predictive role of CAIX for cancer-specific survival [52–55]. In one of the larger series reported from the UCLA, Bui et al. [52] evaluated immunohistochemically the presence of CAIX in the specimens of 321 patients who had undergone nephrectomy for clear cell RCC. The authors showed that low expression of CAIX (<85%) was an independent predictor of cancer-specific survival probabilities, regardless of tumor stage, grade, and ECOG performance status, with metastatic patients with lower level of CAIX having a 3.1-fold higher risk of cancer-related death compared to those with higher expression. In a smaller series of patients with metastatic RCC undergoing interleukin-2 therapy, moreover, Atkins et al. [55] demonstrated that high expression of CAIX predicted a 3.3-fold higher chance to respond to immunotherapy and longer median survival rates. Indeed, a recent publication of the Mayo Clinic team, evaluating 730 patients with clear cell RCC, failed to show an independent predictive role for the expression of CAIX in multivariate analysis [56].

The Mayo Clinic team has recently published several studies on the role of B7-H1 and B7-H4 proteins [57–61]. Members of the B7 family of coregulatory ligands play a central role in the positive and negative regulation of antigen-specific T cell-mediated immune responses. Although expression of such proteins is typically limited to macrophage and lymphoid cells, aberrant B7-H1 and B7-H4 expressions have been shown in several human malignancies, including clear cell RCC, where they could act to impair effective antitumor immunity. Specifically, evaluating fresh-frozen specimens of 196 patients with clear cell RCC, the authors showed the presence of B7-H1 in about 37% of the cases, and those patients harboring B7-H1 were 4.5 times more likely to die from RCC, regardless of pathological stage of the primary tumor, primary tumor size, and presence of metastasis [57]. Interestingly, the same authors reproduced recently similar figures evaluating the expression of B7-H1 by immunohistochemical staining in paraffin-embedded specimens [60]. Moreover, similar data were provided evaluating the expression of B7-H4 on fresh-frozen specimens, showing that patients co-expressing both B7-H1 and B7-H4 were at even higher risk of cancer-related deaths [61].

With regards to genetic markers, several DNA loss and gains have been reported in RCC using comparative

genomic hybridization, including $-6q$, $+17q$, $+17p$, $-9p$, $-13q$, and $-18q$ [62], and we recently showed that the loss of $9p$ was an independent predictor of cancer-specific survival in clear cell RCC, regardless of the Mayo Clinic SSIGN score [63]. Moreover, genomic studies evaluating single nucleotide polymorphisms suggested a possible role for *GNAS1* T393C [64] and *STAT3* [65] polymorphisms.

Gene array analysis has also been used to evaluate candidate markers of response to immunotherapy in RCC. A set of 73 genes, including genes involved in apoptosis, G protein signaling, the ubiquitin–proteasome proteolytic system, chemokines, heat shock proteins, MHC antigens, *PTEN* tumor suppressor, and *CAIX*, has been proposed to identify those patients with a higher chance to respond to immunotherapy [66], but its validation is still lacking.

To date, the role of those genetic and molecular markers has been limited. In the near future, however, some of those proteins could be used, for example, as possible targets for specific imaging and radioimmunotherapies [50]. Moreover, the availability of more efficacious systemic therapies, including the novel tyrosine-kinase inhibitors sunitinib and sorafenib, *MTOR* inhibitors (Temsirolimus), and antibody against VEGF (Bevacizumab), will increase the role of molecular markers, with the aim of predicting the response to different targeted therapies [66].

Integrated prognostic systems

Table 2 summarizes the prognostic factors included in the main integrated systems that are able to predict the risk of progression or survival in patients with localized or metastatic RCC (Table 2) [2, 4–6, 16, 67–71].

Kattan's nomogram

The nomogram proposed by Kattan et al. in 2001 is able to predict the 5-year progression-free survival of patients undergoing radical nephrectomy for non-metastatic RCC, integrating the prognostic value of four different variables: mode of presentation (incidental RCC; RCC with local or systemic symptoms); histological subtypes (clear cell, papillary, or chromophobe RCC); pathological size of the primary tumor (up to a maximum of 20 cm); and pathological stage of the tumor, according to the 1997 version of the TNM staging system (pT1; pT2; pT3a; pT3b-c). Among the variables included in the nomogram, only pathological tumor size ($P = 0.0005$) and histological subtype ($P = 0.03$) were significant in multivariate analysis. In the series of the Memorial Sloan Kettering Cancer Center (MSKCC), which was used to generate the nomogram, the prognostic accuracy was expressed as the area under the curve (AUC), which was as high as 0.74 [2]. The data concerning external

validations of this nomogram are controversial. In a European multicenter study, the accuracy of the Kattan nomogram in the prediction of disease-free survival was evaluated by the *c* index, which turned out to be 0.807 (95% CI 0.777–0.835). However, the prognostic accuracy of the same nomogram in the evaluation of both overall and cancer-specific survival was lower, with *c* index values as high as 0.706 (95% CI 0.681–0.731) and 0.771 (95% CI 0.745–0.795), respectively [72]. A recent paper attempting a further external validation of Kattan nomogram showed lower prognostic accuracy, with *c* index value as low as 0.607 (95% CI 0.576–0.635) [73].

Sorbellini's nomogram

This second nomogram proposed by the MSKCC group was generated to estimate the 5-year disease-free survival probabilities of patients with clear cell RCC only. The following variables were included in the model: pathological size of the primary tumor (up to a maximum of 22 cm); pathological stage of the primary tumor, according to the 2002 version of the TNM staging system (pT1a, pT3a, pT1b, pT2, pT3b); Fuhrman nuclear grade (G1-2, G3, G4); tumor necrosis (present or absent); microvascular invasion (present or absent), and mode of presentation (incidental RCC, RCC with local or systemic symptoms). Among the variables included in the nomogram, only the presence of microvascular invasion ($P = 0.012$), and Fuhrman nuclear grades ($P = 0.002$) were independent predictors of disease-free survival on multivariate analysis. Moreover, the presence of tumor necrosis was surprisingly associated with more favorable cancer-related outcome. The external validation of the nomogram was performed on a series of 200 patients who had undergone radical nephrectomy for clear cell RCC at Columbia University. The value of *c* index was 0.82 [6].

UCLA integrated staging system (UISS)

The UCLA Integrated Staging System is able to stratify the patients with RCC according to pathological stage (TNM, 1997), Fuhrman nuclear grade, and ECOG performance status [68]. The system allows distinguishing the patients with either localized or metastatic RCC into subgroups with low, intermediate, or high risk of progression and mortality [3]. With regards to patients with non-metastatic RCC at the time of the initial diagnosis, the 5-year overall and cancer-specific survival probabilities were as high as 83.8 and 91.1% for the low-risk group; 71.9 and 80.4% for the intermediate-risk group; and 44 and 54.7% for the high-risk group, respectively [3]. In patients with metastatic RCC, the 2-year overall and cancer-specific survival probabilities were as high as 63 and 65% for the low-risk group; 40.5

Table 2 Prognostic factors included in the principal mathematical models to predict prognosis in patients with localized or metastatic RCC

Author	Cases	Stage	Therapy	Histotype	Endpoint	Variables
Yaycioglu et al. [67]	296	N0 M0	Radical nephrectomy	Not applicable	DFS	Symptoms Clinical Tumor Size
Kattan et al. (MSKCC) [2]	601	N0 M0	Radical nephrectomy	Conventional Papillary Chromophobe	DFS	Symptoms Histotype Pathological tumor size pT (1997)
Zisman et al. (UCLA) [68]	661	All	Radical nephrectomy	All	OS	TNM stage Performance status ECOG Nuclear Grading
Frank et al. (Mayo Clinic) [5]	1,801	All	Radical nephrectomy	Conventional	CSS	pT (1997) pN (1997) M Pathol. Size ($\leq 5 / > 5$ cm) Nuclear Grading Necrosis
Morzer et al. (MSKCC) [4]	463	N +M +	Interpheron-alfa	All	OS	Performance status LDH Hemoglobin Serum Calcium Time diagnosis-therapy
Cindolo et al. (Multicentric European Group) [69]	660	N0 M0	Radical nephrectomy	Not applicable	DFS	Symptoms Clinical Size
Leibovich et al. (Mayo Clinic) [70]	1671	N0 M0	Radical nephrectomy	Conventional	DFS	pT (1997) pN (1997) Pathol. Size ($\leq 10 / > 10$ cm) Nuclear Grading Necrosis
Leibovich et al. (Mayo Clinic) [71]	727	M +	Radical nephrectomy	Conventional	CSS	Symptoms Bone metastasis Liver metastasis Multiple metastasis Yrs from nephrectomy to metastasis Complete resection of metastatic RCC Tumor thrombus Nuclear grade Necrosis
Sorbellini et al. (MSKCC) [6]	833	N0 M0	Partial or radical nephrectomy	Conventional	DFS	Symptoms Pathological size pT (2002) Nuclear Grade Necrosis Vascular Invasion
Karackiewicz et al. (Multicentric) [16]	2,530	All	Partial or radical nephrectomy	All	CSS	Symptoms Pathological size pT (2002) N (2002) M (2002) Nuclear grade

and 40.9% for the intermediate-risk group; and 10.1 and 10.5% for the high-risk group, respectively [3].

The UCLA integrated staging system was initially validated in a series of non-metastatic RCC operated on in three different academic centers: Nijmegen (The Netherlands), MD Anderson, Houston (Texas, US), and UCLA, Los Angeles (California, US). The values of *c* index for each participating center were 0.79, 0.86, and 0.84 [74]. Patard et al. [30] performed a further external validation in a multicenter study including 4,202 treated in eight different American and European academic centers. In 3,119 patients with non-metastatic RCC, the values of *c* index ranged from 0.765 to 0.863, while in the 1,083 patients with metastatic RCC, the values of *c* index ranged from 0.644 to 0.776. The UISS was used to select high-risk patients who were to be included in two randomized controlled trials (ASSURE and STAR) that evaluated the efficacy of sunitinib and sorafenib as adjuvant therapies.

Karakiewicz's nomogram

In 2007, Karakiewicz et al. [7] published a new nomogram, which was able to estimate the 1, 2, 5, and 10-year cancer-specific survival probabilities of patients undergoing partial or radical nephrectomy for RCC. The following variables were included in the nomogram: pathological stage of the primary tumor (T), lymph node involvement (N), presence of distant metastases (M), pathological size of the primary tumor, Fuhrman nuclear grade, and presence of symptoms. The nomogram was generated analyzing a series of 2,530 patients and validated on an external cohort of 1,422 patients with RCC. The prognostic accuracy of the nomogram in the prediction of 1, 2, 5, and 10-year cancer-specific survival was as high as 87.8, 89.2, 86.7, and 88.8%, respectively. In the cohort of patients used for the external validation, the prognostic accuracy for the estimation of 2 and 5-year probabilities was significantly higher than for UCLA integrated staging system.

Stage, size, grade, and necrosis (SSIGN) score

In 2002, Frank et al. [5] proposed a different algorithm to predict the cancer-specific survival of patients with clear cell RCC undergoing radical nephrectomy. Differing from all the other models, this algorithm included only pathological variables. The prognostic score was based on the variables, which turned out to be independent predictors of cancer-specific survival on multivariate analysis: pathological stage of the primary tumor (pT, 1997); loco-regional lymph node involvement (N); presence of distant metastasis (M); pathological size of the primary tumor higher than or equal to 5 cm; Fuhrman nuclear grade; and presence of microscopic tumor necrosis.

According to the different scores, the patients were stratified into ten different subgroups with different cancer-related prognosis. The 10-year cancer-specific survival probabilities were as high as 97.1% for those patients with a score of "0 or 1"; 85.3% for those with score of "2"; 77.9% for those with a score of "3"; 66.2% for those with a score of "4"; 50% for those with a score of "5"; 38.8% for those with a score of "6"; 28.1% for those with a score of "7"; 12.7% for those with a score of "8"; 14.8% for those with a score of "9"; and 4.6% for those with a score "≥10". The value of *c* index was 0.839 [5]. In the external validation, the *c* index was as high as 0.88 [75].

A modified version of the SSIGN score was proposed by Leibovich et al. [70] with the aim of predicting the disease-free survival of patients undergoing radical nephrectomy for clear cell RCC. The following variables were included in the score: pathological stage of the primary tumor (pT, 2002); loco-regional lymph node involvement (N); pathological size of the primary tumor (< vs. ≥10 cm); Fuhrman nuclear grade, and presence of microscopic tumor necrosis.

According to the different scores, the authors suggested that three subgroups with different risks of progression may be distinguished: low risk (scores from 0 to 2), intermediate risk (scores from 3 to 5), and high-risk group (scores higher than or equal to 6). The value of *c* index of the score was as high as 0.819 [70]. Recently, the Mayo Clinic group presented a dynamic version of the SSIGN score, which was able to predict CSS taking into account the disease-free interval from surgery to follow-up. In this study, 1-, 5-, and 10-year CSS was predicted in patients after 6, 12, 24, 36, and 60 months after radical nephrectomy, demonstrating a decrease in the risk of cancer death during follow-up [76]. Finally, the SSIGN has been used to select patients who are to be recruited into the SORCE trial that evaluates the efficacy of sorafenib as an adjuvant treatment in intermediate and high-risk localized RCC.

Prognostic scores for patients with metastatic RCC

The prognostic scores proposed by Motzer to predict the survival rates of patients with metastatic RCC are based only on non-pathological variables. In 2002, Motzer et al. [4] suggested that patients with RCC, who are candidates to first-line systemic therapy, may be stratified according to five variables, which were significant on multivariate analysis: Karnofsky performance status lower than 80%; LDH value higher than 1.5 times the upper limit of normal; serum hemoglobin lower than 13 g/dL for males and 11.5 g/dL for females; corrected serum calcium higher than 10 mg/dl; and interval shorter than 1 year between diagnosis of RCC and beginning of the therapy with interferon- α . The patients were distinguished into low, intermediate, and high risk according to the presence of no, only one or two, or more than two risk

factors. The median survival was as long as 30 months in the low-risk, 14 months in the intermediate-risk, and 5 months in the high-risk group, respectively. More recently, the same model was used to predict the survival rates of patients with local or distant recurrences after radical nephrectomy. In this setting, the median survival was 76 months in the low-risk, 25 months in the intermediate risk, and 6 months in the high-risk group, respectively [77].

In those patients who were candidates for second-line systemic therapies, the prognostic score did not include the interval between initial diagnosis of RCC and the beginning of systemic therapies, as well as the LDH levels. Consequently, the patients were subclassified into low risk (score equal to 0), intermediate risk (score equal to 1), and high risk (score higher than or equal to 2). The median survival was 22 months in the low-risk, 12 months in the intermediate-risk, and 5.4 months in the high-risk group, respectively [13]. The model by Motzer et al. has been used to stratify the results of several trials evaluating the efficacy of immunotherapy [78–80] or targeted therapies [81–84] in metastatic patients.

A further scoring algorithm for metastatic clear cell RCC was proposed by Leibovich et al. in [71]. Specifically, the authors evaluated 727 patients who had distant metastases at the time of nephrectomy or developed metastases during follow-up after surgery. About 83% of the patients experienced cancer-related deaths. Using a multivariate model, the authors generated a scoring system, which included the following variables: constitutional symptoms at presentation, bone metastases, liver metastases, multiple metastases, years from nephrectomy to metastases, complete resection of metastatic RCC, tumor thrombus, nuclear grade, and coagulative tumor necrosis. The c index for the scoring algorithm was 0.671.

Conclusions

The impact of traditional prognostic factors in estimation of the risk of progression and survival of patients with RCC has been adequately evaluated during the last years, and several large and methodologically consistent studies have been published. The chance to integrate the data derived from each prognostic factor into prognostic algorithms and scores has allowed to improve significantly the stratification of the prognosis of the patients with RCC. Although the TNM is the most commonly applied staging system, integrating staging systems should be used to design the RCTs, which will evaluate the efficacy of the new systemic therapies in either neoadjuvant, adjuvant, or salvage treatments of patients with RCC.

The improvement of the prognostic tools as well as the clearer comprehension of the molecular mechanisms,

which lead to development, and progression of RCC can provide a valid rationale to assess the prognostic role of several specific molecular markers. The expected aim is the improvement of the currently available prognostic systems through the inclusion of molecular and genetic variables. In the meanwhile, it is desirable that new prognostic models should predict the response to the main target therapies.

Most of the currently available prognostic algorithms and scores have been developed on retrospective series. The prospective validation of these tools within large phase III studies or specific clinical trials might be one of the next challenges.

Conflict of interest statement There is no conflict of interest.

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