Review

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Mathematical Models for Prognostic Prediction in Patients with Renal Cell Carcinoma

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Key Words
Renal cell carcinoma · Algorithms · Nomograms · Prognostic factors · Prognosis · Mathematical models

Abstract
Objectives: The objectives of this study are to catalogue all models developed to predict survival of RCC patients and to identify the ones to be used in different situations. ***Methods:*** A systematic review was performed searching with a free text and MeSH strategy 3 electronic databases. For each model, the following parameters were identified: number, features of the patients; evaluation endpoints; clinical and/or pathological variables included; concordance indexes (cI). ***Results:*** The research retrieved 156 records. Eleven articles proposed new models, 5 articles external validations. We retrieved 2 mathematical models including clinical variables only (Yaycioglu, cI 0.651; Cindolo, cI 0.672); 2 algorithms including also pathological variables (SSIGN, cI 0.819; UISS, cI 0.79–0.84), 5 nomograms (Kattan, cI 0.76–0.86; Sorbellini, cI 0.82; Kim 2004, cI 0.79, Kim 2005, cI 0.68; Karakiewicz, cI 0.86); 2 algorithms for patients with metastatic disease (Motzer, Leibovich). ***Conclusions:*** The SSIGN was the most accurate algorithm for conventional RCC, while the UISS allowed the evaluation of patients regardless of tumor histotype. The Sorbellini nomogram is applicable only for patients with conventional RCC, while the Kattan and Karakiewicz nomograms also provide information for other histotypes. Metastatic patients can be evaluated with Leibovich and Motzer algorithms. Two models combine molecular markers and clinical features (Kim 2004–2005).

Introduction

In patients with renal cell carcinoma (RCC), the study of prognostic factors improves the accuracy of the information provided during counseling and the appropriateness of postoperative follow-up planning. Moreover, the stratification of patients according to the clinical and pathological features is fundamental to define inclusion and exclusion criteria and to accurately evaluate the results of randomized clinical trials (RCTs). Considering the wide number of RCTs that will be designed and conducted in the next years to evaluate the efficacy of the new antiangiogenetic drugs in RCC patients, the issue concerning prognostic factors gains further importance [1].

Modality of presentation, performance status, pathological stage (TNM), tumor size, nuclear grading, and

Take-home message: Nomograms and algorithms developed for RCC prognostication provide higher accuracy than the single prognostic variables. Nevertheless, they need continuous updates according to the variations in staging and prognostic classifications.

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microscopic tumor necrosis are the main variables able to independently predict survival of patients with RCC. Up to date, the independent value of tumor histological subtype is still under debate [2, 3].

Since 2001, several mathematical models have been projected with the objective to develop prognostic tools containing all available clinical and pathological information. Specifically, algorithms allow the stratification of patients into prognostic categories; on the contrary, nomograms are a graphical representation of a multivariate analysis model, calculating with a punctual precision the survival probabilities of each single patient. Even though mathematical models provide a higher accuracy than single variables, their use in clinical practice and in research trials is not currently widespread.

The available mathematical models can be distinguished according to their structure, to evaluated endpoint, population from which they have been developed, and, most of all, clinical and/or pathological included variables. These aspects justify different clinical applications.

The objectives of the present systematic review of the literature are to catalogue all models developed to predict survival of patients with RCC and to critically analyze their features with the aim of identifying the ones to be used in different clinical situations or RCTs.

Materials and Methods

The literature review was performed in April 2007 using Embase, MEDLINE, and Web of Science. The MEDLINE search used a complex search strategy including both 'MeSH' (Medical Subject Heading) and free text protocols. Specifically, the MeSH search was conducted by combining the following terms retrieved from the MeSH browser provided by MEDLINE: 'Nomograms', 'Kidney neoplasms', 'Nomograms' and 'Algorithms'. Multiple free text searches were performed applying singularly the following terms: 'Renal Cell Carcinoma', 'Kidney Cancer', 'RCC', 'Nomogr*', 'Algorit*', 'Mathematical models'. Subsequently, the searches were pooled. No limits were used to restrict the research.

The searches on Embase and Web of Science used only the free-text protocol, with the same key words. Subsequently, the queries were pooled without the application of any limit. Furthermore, the Cochrane database of systematic review was browsed for records regarding Renal Cell Carcinoma and the abstract books of the American Urological Association (AUA) and European Association of Urology (EAU) annual meetings from 2000 to 2005 were hand-searched for studies concerning the topic of the review. In addition, other significant studies cited in the reference lists of the selected papers were considered. Two authors reviewed all retrieved abstracts and selected those relevant for the study.

The selected articles were classified in: (1) proposals of mathematical models, and (2) external validations of existent mathematical models.

For each identified predictive mathematical model the following parameters were identified: number and features of the patients used for the statistical construction of the model; assessed endpoint; included clinical and/or pathological variables; concordance index (*c* index) value of the initial study and of the eventual external validations.

The prognostic accuracy of the different prognostic models has been evaluated on the basis of the *c* index reported by the initial or by the following validation studies. A *c* index between 0.50 and 0.70 expresses a low prognostic accuracy, between 0.71 and 0.90 a moderate accuracy, and >0.90 a high accuracy [4].

Results

The research provided 172 records. From the initial search the authors selected 13 articles providing proposals for new mathematical predictive models and 5 articles dealing with their external validation. Table 1 shows the selected mathematical models. Table 2 shows the *c* index values of each available mathematical model reported at the initial validation study according to the different endpoints.

Predictive Models Based on Clinical Variables

In 2001, Yaycioglu et al. [5] proposed a mathematical model able to calculate the risk for disease recurrence after radical nephrectomy according to modality of presentation and clinical tumor size. In the model the risk for relapse is represented by the following formula: $R_{rec} = 1.55 \times$ presentation (0 = asymptomatic; 1 = symptomatic) + 0.19 × clinical size (in centimeters). Accordingly, the patients can be subdivided in a low-risk group in the case of scores ≤3.0 and in a high-risk group in the case of scores >3.0. Specifically, patients with a low risk of relapse had a 5-year cancer-specific survival (CSS) probability of 92%, which is significantly higher than the 57% of the patients belonging to the high-risk group.

In 2003, Cindolo et al. [11] proposed a similar biostatistical model able to predict the disease-free survival (DFS) of patients undergoing radical nephrectomy. In this case, the formula was: $R_{rec} = 1.28 \times$ presentation (asymptomatic = 0; symptomatic = 1) + (0.13 × clinical size). Differently from the previous model, the cut-off used to stratify patients into groups with different prognoses was 1.2. In details, patients with a score ≤1.2 presented a 5-year DFS of 93%, significantly better than the 68% of the patients with a score >1.2.

Table 1. Mathematical models developed to predict survival of patients with RCC

Author	Cases	Stage	Therapy	Histotype	Endpoint	Variables
Yaycioglu, 2001 [5]	296	N0 M0	Radical nephrectomy	Not applicable	DFS	Symptoms Clinical tumor size
Kattan, 2001 (MSKCC) [6]	601	N0 M0	Radical nephrectomy	Clear cell papillary chromophobe	DFS	Symptoms Histotype Pathological tumor size pT (1997)
Zisman, 2001 (UCLA) [7]	661	All	Radical nephrectomy	All	OS	TNM stage Performance status ECOG Nuclear grading
Zisman, 2002 (UCLA) [8]	814	All	Radical nephrectomy	All	OS CSS DFS	TNM stage Performance status ECOG Nuclear grading
Frank, 2002 (Mayo Clinic) [9]	1,801	All	Radical nephrectomy	Clear cell	CSS	pT (1997) pN (1997) M Pathol. size (≤5/>5 cm) Nuclear grading Necrosis
Motzer, 2002 (MSKCC) [10]	463	N+/M+	Interferon-α	All	OS	Performance status LDH Hemoglobin Serum calcium Time diagnosis-therapy
Cindolo, 2003 (Multicentric European Group) [11]	660	N0 M0	Radical nephrectomy	Not applicable	DFS	Symptoms Clinical size
Leibovich, 2003 (Mayo Clinic) [12]	1,671	N0 M0	Radical nephrectomy	Clear cell	DFS	pT (1997) pN (1997) Pathol. size (≤10/>10 cm) Nuclear grading Necrosis
Leibovich, 2003 (UCLA) [13]	173	N+/M+	Radical nephrectomy + immunotherapy (IL-2)	All	CSS	pN Constitutional symptoms Metastasis site Sarcomatoid features Serum TSH
Kim, 2004 (UCLA) [14]	318	All	Radical nephrectomy	Clear cell	CSS	M stage ECOG PS pT (2002) CA9 p53 Vimentin
Kim, 2005 (UCLA) [15]	150	N+/M+	Radical nephrectomy	Clear cell	CSS	ECOG PS pT (2002) CA9 p53 Vimentin PTEN

Table 1 (continued)

Author	Cases	Stage	Therapy	Histotype	Endpoint	Variables
Sorbellini, 2005 (MSKCC) [16]	833	N0 M0	Partial or radical nephrectomy	Conventional	DFS	Pathological size pT (2002) Nuclear grading Necrosis Vascular invasion Symptoms
Karakiewicz, 2007 [17]	2,530 + 1,422	All	Partial or radical nephrectomy	All	CSS	pT (2002) Nodal status Metastatic status Tumor size Fuhrman grade Symptoms

DFS = Disease-free survival; LDH = lactate dehydrogenase; IL-2 = interleukin-2; CSS = cancer-specific survival; TSH = thyroid-stimulating hormone; ECOG PS = performance status ECOG; CA9 = carbonic anhydrase 9; PTEN = phosphatase and tensin homologue deleted on chromosome 10.

Table 2. *c* index values reported in initial or validation studies according to the different endpoints

Predictive model	DFS	CSS	OS
Yaycioglu, 2001 (Johns Hopkins) [5]	0.651 [18]	0.629 [18]	0.589 [18]
Cindolo, 2003 (Multicentric European Group) [11]	0.672 [18]	0.648 [18]	0.615 [18]
Kattan, 2001 (MSKCC) [6]	0.807 [18] 0.607 [19]	0.771 [18]	0.706 [18]
UISS, 2002 (UCLA) [8]		0.79–0.84 [20][1]	0.76–0.86 [21][1] 0.64–0.77 [21][2]
SSIGN, 2002 (Mayo Clinic) [9]	0.819 [12]	0.83 [9] 0.88 [22]	
Kim, 2004 (UCLA) [14]		0.79 [14]	
Kim, 2005 (UCLA) [15]		0.68 [15]	
Sorbellini, 2005 (MSKCC) [16]	0.82 [16]		
Karakiewicz 2007 (Multicentric European Group) [17]		0.86 [17]	

[1] Validation only for non-metastatic patients. [2] Validation only for metastatic patients.

The prognostic accuracy of these two models has been verified in a multicentric study analyzing 2,404 patients undergoing radical nephrectomy in 6 different European centers. The *c* index predicting DFS for the Yaycioglu model resulted in 0.651 (95% CI 0.609–0.691). Lower performances were reported for CSS (*c* index 0.629) or overall survival (OS) (*c* index 0.589). Higher values were reported for the model by Cindolo et al. [18]. The *c* index for the DFS was 0.672 (95% CI 0.640–0.704), while for the CSS and OS it was 0.648 and 0.615, respectively.

Kattan Nomogram

The Kattan nomogram was generated to predict recurrence-free survival using the prognostic information of 601 patients undergoing radical nephrectomy for non-metastatic RCC at the MSKCC between 1989 and 1998 (fig. 1). In the studied population the 5-year DFS resulted in 86%. The multivariate analysis in this series highlighted that only tumor size (p = 0.0005) and tumor histological subtype (p = 0.03) were able to independently predict the DFS. Nevertheless, all the other statistically insignifi-

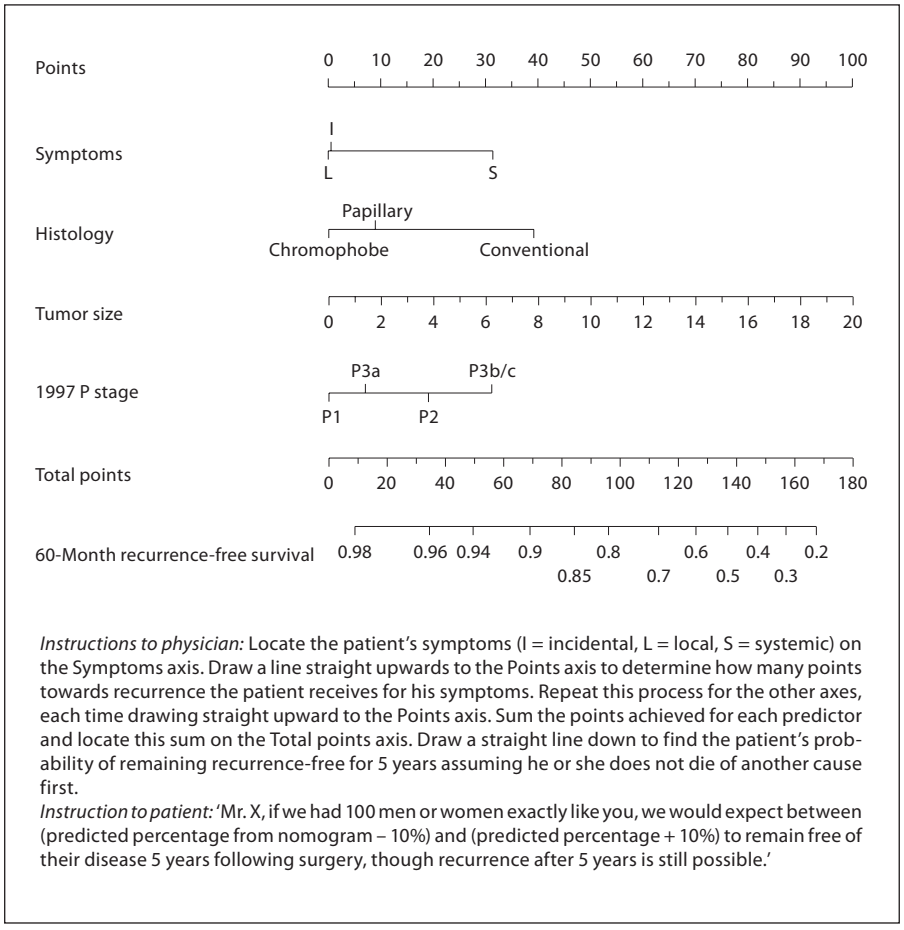

Fig. 1. Kattan nomogram: postoperative prognostic nomogram for RCC [reproduced from 6, with permission].

cant variables were included in the nomogram. The 5-year DFS was estimated according to: (1) modality of presentation (asymptomatic, with local or systemic symptoms); (2) tumor histotype (chromophobe, papillary and conventional RCC); (3) pathological tumor size (up to a 20-cm maximum); (4) pathological stage of the primary tumor according to 1997 TNM (pT1; pT2; pT3a; pT3b-c) [6]. The internal validation of the nomogram was performed with the bootstrapping method. The area under the curve was 0.74. A higher accuracy was reported by the multicentric study by Cindolo et al. [18]. In that European series, the *c* index for the DFS was 0.807 (0.777–0.835). Moreover, *c* indexes for CSS and OS according to the Kattan nomogram resulted in 0.771 (0.745–0.795) and 0.706 (0.681–0.731), respectively. However, a more recent external validation of the nomogram highlighted a lower prognostic accuracy with a *c* index of 0.607 (95% CI 0.576–0.635) [19]. The peculiar design of the nomogram, developed to predict recurrence-free survival only, limits its clinical use.

UCLA Integrated Staging System (UISS)

In 2001, Zisman et al. [7] proposed to reclassify RCC patients in 5 different categories on the basis of the information coming from ECOG performance status, Fuhrman nuclear grades and pathological stage according to the 1997 version of the TNM. This integrated system was generated analyzing the overall survival of 661 patients undergoing radical nephrectomy at the UCLA. Patients included in the initial analysis included all RCC histological subtypes. Their 5-year overall survival probabilities were 95% in group I, 67% in group II, 39% in group III, 23% in group IV, and 0% in group V.

The application of the UISS integrated system to a population of 468 patients undergoing radical nephrectomy for non-metastatic RCC allowed the identification of 3 groups with low, intermediate and high risk for progression and mortality. Similarly, the application of the UISS to a population of 346 patients with metastatic RCC allowed the identification of 3 groups with different prognoses [8]. In non-metastatic patients, 5-year OS and CSS

Table 3. UISS: variables and risk groups in non-metastatic and metastatic patients (adapted from Zisman et al. [8])

Non-metastatic patients

T stage	1				2	3				4
Grade	1–2		3–4		↓	1		>1		↓
ECOG PS	0	≥1	0	≥1		0	≥1	0	≥1	
Risk	low	intermediate (int)							high	

Metastatic patients

T stage	N1M0	N2M0/M1							
Grade	↓	1		2		3		4	
ECOG PS		0	≥1	0	≥1	0	≥1	0	≥1
Risk	low		int	low	int				high

Table 4. Stage size grade and necrosis score (adapted from Frank et al. [9])

Feature		Score (CSS)
T stage	pT1a	0
	pT1b	0
	pT2	1
	pT3a	2
	pT3b	2
	pT3c	2
	pT4	0
N stage	pNx	0
	pN0	0
	pN1	2
	pN2	2
M stage	pM0	0
	pM1	4
Tumor size, cm	<5	0
	≥5	2
Fuhrman nuclear grade	1	0
	2	0
	3	1
	4	3
Necrosis	Absent	0
	Present	2

resulted in 83.8 and 91.1% in the low, 71.9 and 80.4% in the intermediate, and 44 and 54.7% in the high-risk group, respectively. Moreover, the 5-year DFS resulted in 91.4% for low-risk patients, 64% for intermediate-risk ones, and 37.3% for high-risk ones. In patients with metastatic RCC, 2-year OS and CSS were 63 and 65% in the low-risk group, 40.5 and 40.9% in the intermediate-risk group, and 10.1 and 10.5% in the high-risk group, respectively. The UISS groups and the strategy used to assign patients with or without metastases to a risk group are reported in table 3.

The UCLA algorithm was validated in 2003 by Han et al. [20] using a population of patients with non-metastatic RCC treated at 3 referral centers: Njimegen (the Netherlands), MD Anderson, Houston (Tex., USA), and UCLA, Los Angeles (Calif., USA). The *c* index of each center resulted in 0.79, 0.86 and 0.84, respectively. A larger external validation has been recently performed by Patard et al. [21] in a multicentric study including 4,202 patients from 8 academic centers: Rennes, Saint Etienne and Creteil (France); Napoli and Verona (Italy), Nijmegen (The Netherlands), M.D. Anderson and UCLA (USA). In the 3,119 non-metastatic patients, the *c* index of the single centers ranged between 0.644 and 0.776. Notably, the UISS system will be used to select patients in 2 phase III adjuvant trials: ECOG 2805, comparing placebo versus Sorafenic versus Sutent, and S-TRAC, comparing placebo versus Sutent in high-risk UISS patients.

Stage, Size, Grade and Necrosis (SSIGN) Score

In 2002, Frank et al. [9] proposed a prognostic algorithm to predict CSS of patients with conventional RCC. The model was developed from a dataset of 1,801 patients undergoing radical nephrectomy at the Mayo Clinic between 1979 and 1998, including only the variables significant in the multivariate analysis. In particular, the 1997 version of the TNM staging system ($p < 0.001$), pathological size of the primary tumor ≥5 cm ($p < 0.001$), Fuhrman nuclear grades ($p < 0.001$) and the presence of microscopic tumor necrosis ($p < 0.001$) were the variables able to independently predict CSS. The rules to assign the score are reported in table 4. The authors described 10 categories of patients with different CSS. In particular, 10-year CSS was 97.1% in patients with a score of '0–1', 85.3% in those with a score of '2', 77.9% in those with a score of '3', 66.2% in those with a score of '4', 50% in those with a score of '5', 38.8% in those with a score of '6', 28.1% in those with a score of '7', 12.7% in those with a score '8', 14.8% in those with a score of '9', and finally 4.6% in those with a score '≥10'. The *c* index of this algorithm was 0.839 [9].

In 2003, a similar algorithm was proposed by the same group with the aim to estimate DFS in 1,671 patients undergoing radical nephrectomy for conventional, non-metastatic RCC. The algorithm included pathological

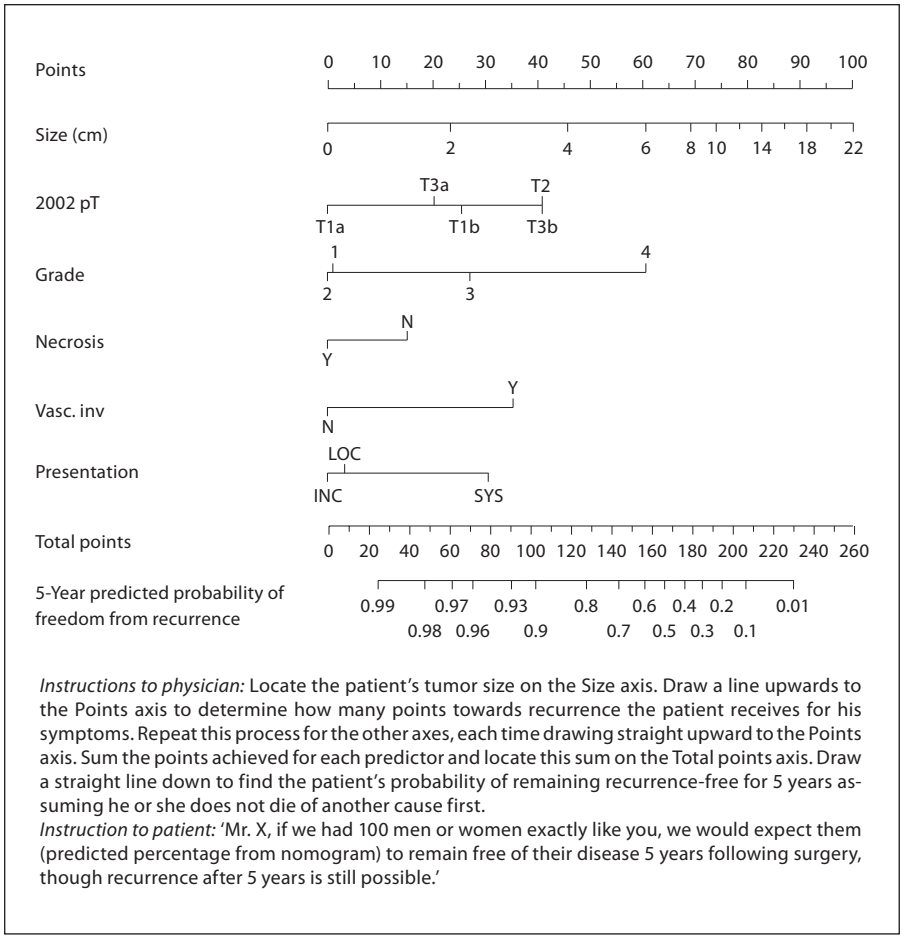

Fig. 2. Sorbellini nomogram [reproduced from 15, with permission].

stage according to the 2002 version of the TNM staging system (pT1a = 0; pT1b = 2; pT2 = 3; pT3a = 4; pT3b = 4; pT3c = 4; pT4 = 4); locoregional lymph nodal status (pNx = 0; pN0 = 0; pN1 = 2; pN2 = 2); pathological size of the primary tumor (<10 cm = 0; ≥10 cm = 1); Fuhrman nuclear grades (grade 1 = 0; grade 2 = 0; grade 3 = 1; grade 4 = 3) and presence of microscopic tumor necrosis (absent = 0; present = 1). The authors identified 8 categories with different prognoses. Ten-year DFS resulted in 96.1% in patients with a score of '0–1', 88.5% in those with a score of '2', 78.6% in those with a score of '3', 63.2% in those with a score of '4', 54.8% in those with a score of '5', 29.8% in those with a score of '6', 24.7% in those with a score of '7', and 10.2% in those with a score '≥8'. Clustering the groups, the authors proposed to stratify patients into 3 different categories: low (score 0–2), intermediate (score 3–5) and high risk of progression (score ≥6). The *c* index coming out from the internal validation of this algorithm was 0.819 [12]. The SSIGN algorithm was validated in 2006 by Ficarra et al. [22] in an Italian series of 388 patients undergoing radical and partial nephrectomy for conventional RCC between 1986 and 2000. In this case, the *c* index was 0.88. In this study the patients were finally subdivided into 5 categories with different prognoses, with scores of 0–2, 3–4, 5–6, 7–9, and ≥10.

Recently, the Mayo Clinic group presented a dynamic version of the SSIGN score, 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, 60 months after radical nephrectomy, demonstrating a risk of cancer death decreasing during follow-up [23].

Finally, the SSIGN score will be used to select patients for the SORCE trial, evaluating placebo versus Sorafenib 1 year versus Sorafenib 3 years in intermediate- and high-risk SSIGN patients.

Table 5. Scores of patients undergoing radical nephrectomy and IL-2 according to the Leibovich algorithm [13]

Feature		Score
Constitutional symptoms at presentation	No	0
	Yes	2
Bone metastases	No	0
	Yes	2
Liver metastases	No	0
	Yes	4
Multiple metastases	No	0
	Yes	2
Years from nephrectomy to metastases	≥2	0
	<2	3
	0[1]	1
Complete resection of metastatic RCC	No	0
	Yes	–5
Tumor thrombus	None or level 0	0
	Level I, II, III, IV	3
Fuhrman nuclear grade	1, 2 or 3	0
	4	3
Coagulative tumor necrosis	No	0
	Yes	2

[1] Metastases at nephrectomy.

Sorbellini Nomogram

The Sorbellini nomogram was proposed from the MSKCC group in 2005 to calculate the 5-year DFS of patients undergoing surgical treatment for conventional RCC (fig. 2). The nomogram was generated using data of 833 patients undergoing radical or partial nephrectomy between 1989 and 2002. The multivariate analysis showed only microvascular invasion (p = 0.012) and Fuhrman nuclear grades (p = 0.002) to be independent predictors for DFS. Nevertheless, the following variables were used to develop the nomogram: (1) pathological size of the primary tumor (up to 22 cm); (2) local extension of the primary tumor according to the 2002 TNM version (pT1a; pT3a; pT1b; pT2; pT3b); (3) Fuhrman nuclear grading (G1–2; G3; G4); tumor necrosis (absent; present), and the modality of presentation (incidental; local symptoms; systemic symptoms). The external validation of the nomogram was performed in the same study using the data of 200 patients undergoing radical nephrectomy for conventional RCC at the Columbia University. The *c* index was 0.82 [16].

Karakiewicz Nomogram

Collecting patients from a multicentric European database, the nomogram by Karakiewicz et al. [17] has been recently generated in order to predict 1-, 2-, 5-, and 10-year CSS of patients undergoing surgical treatment for all stages RCC. The nomogram was developed from a series of 2,530 patients and externally validated on further 1,422 patients. In multivariate analysis, the following independent predictors of survival were identified: pT (2002), N, and M stages, tumor size, Fuhrman grade, histological type, age and symptom classification. All of these variables except for age were included in the nomogram. The model proved to have a high prognostic accuracy (0.86 *c* index), which was significantly higher than the one of the UISS (p = 0.007 at 2-year and p = 0.02 at 5-year CSS, respectively).

Algorithm for the Prediction of Survival after Nephrectomy and Immunotherapy (IL-2)

In 2003, Leibovich et al. [13] proposed an algorithm able to predict CSS in 173 patients with metastatic RCC undergoing radical nephrectomy and immunotherapy with interleukin 2 (IL-2). On multivariate analysis, status of regional lymph nodes (p = 0.002), presence of systemic symptoms (p = 0.005), metastatic site (multiple metastases, non-skeletal or non-pulmonary metastases) (p < 0.0001), presence of a sarcomatoid component (p = 0.003), and TSH values (p = 0.03) were the variables able to independently predict CSS. On the basis of the results of multivariate analysis, the authors developed a score to stratify patients in low (score 0), intermediate (score 1–3), and high mortality risk (score >3) (table 5). Five-year CSS probabilities were 41% in the low and 19% in the intermediate-risk group. One-year survival probability of high-risk patients was 1%.

Prognostic Model for Metastatic RCC

In 2001, Motzer et al. [10] proposed a prognostic stratification of metastatic RCC patients undergoing interferon-α immunotherapy. Specifically, the retrospective analysis of the clinical data of 463 patients recruited in 6 previous prospective trials highlights the negative prognostic impact of a low Karnofsky performance status, high LDH values, low hemoglobinemia, high serum calcium, and a time of >1 year between the RCC diagnosis and the beginning of interferon therapy. Each patient was assigned to a group at low, intermediate and high risk, according to the absence of risk factors or to the presence of 1–2 risk factors, or >2 risk factors, respectively. Median survival was 30 months in the first group, 14 months in the second one, and 5 months in the third one. The model was validated by Mekhail et al. [24] in 2005 on a series 353 naive metastatic RCC patients treated at the Cleve-

land Clinic Foundation. In this study, median survival resulted in 28, 14, and 4 months for the low-, intermediate- and high-risk group, respectively. More recently, Motzer's prognostic model was used to predict survival in patients with local and/or distant relapse after radical nephrectomy for RCC. In this case, median survival resulted in 76 months for low, 25 months for intermediate, and 6 months for high-risk patients [25].

Multimarker Prognostic Models

In 2004, Kim et al. [14] from the UCLA studied the possibility to predict prognosis using molecular markers. In their study, the authors included clinical, pathological and molecular data coming out from the records of 318 patients with clear cell RCC of all stages, using tissue arrays and immunohistochemical staining for the molecular analysis. Two multivariate models were constructed: the first one containing molecular markers only (carbonic anhydrase 9, p53, vimentin and gelsolin) and metastatic status as covariate; the second one included a combination of molecular markers with other clinical and pathological variables (carbonic anhydrase 9, p53, vimentin, metastatic status, T stage and ECOG performance status). According to their results, the model combining clinical and molecular variables performed better than the TNM staging system and than the UISS for the prediction of prognosis, with a higher *c* index (0.79 vs. 0.73 and 0.75, respectively). The same authors [15] proposed an analogue model for metastatic RCC patients, reporting a *c* index of 0.68, significantly higher than the UISS *c* index (0.62) in their series.

The limited availability of such molecular markers is the most important drawback of this model.

Discussion

The mathematical models used for prognostic prediction in RCC patients differ in structure, clinical and/or pathological variables included, population of patients used for the validation, and different endpoint of evaluation.

According to their structure, mathematical models are classified into nomograms and algorithms. The former represent graphically the results of multivariate analysis. They allow to calculate the punctual survival of patients undergoing radical nephrectomy for RCC. They provide specific information for the single patient, without a stratification in prognostic groups. For this reason, their natural application is for postoperative counseling of patients undergoing radical or partial nephrectomy or for follow-up planning. On the contrary, algorithms classify patients into prognostic categories. They are helpful tools not only in the planning of postoperative follow-up, but also in the design and interpretation of the results of RCTs.

Mathematical models include clinical variables, pathological ones, or more frequently both of them. The models including clinical variables only are characterized by a prognostic accuracy significantly lower than the ones using pathological variables (table 2).

Between the two models including clinical variables only, the algorithm by Cindolo et al. [11] is slightly more accurate than the one by Yaycioglu et al. [5] in the prediction of DFS, CSS and OS.

One of the most controversial points concerning the models including pathological variables is the role of tumor histotype. Some predictive models have different scores according to the different histotypes [6]; others have been developed exclusively for clear cell RCC [9, 16]; others do not take into account histotype as a discriminating variable [7, 13]. This variability is an expression of the literature controversies on the prognostic impact of tumor histotype. In 2003, Cheville et al. [26] reported a CSS worse for patients with conventional RCC than for patients with papillary or chromophobe tumors. In Mayo Clinic series, these differences were statistically significant also after correction for pathological stage or nuclear grading. These data support the strategy to develop different mathematical models for different histotypes [9, 16]. On the contrary, in a multicentric international study, Patard et al. [3] did not confirm the independent predictive value of tumor histotype on the prognosis of RCC patients. This study supports models that do not take into account tumor histotype. The absence of correlation between morphogenetic features and statistical results in histotype prognostic evaluations can be explained by the incorrect histotype assignation (more common in cases diagnosed before the publication of the Heidelberg classification, adopted by UICC/AJCC in 1997 [27]) and, from a statistical point of view, by the predominance of conventional RCC cases and events [2, 28].

Another relevant aspect emerging from literature is the different prognostic impact that some pathological variables might have in different histotypes. Specifically, Fuhrman nuclear grade and tumor necrosis have a different prognostic meaning according to the different histotypes [29–31]. On the basis of these last considerations, the use of Fuhrman nuclear grade in the UISS could be inappropriate. For the same reasons, Fuhrman nuclear

grade has not been contemplated among the variables of the Kattan nomogram [6].

A further critical aspect related to the construction of mathematical models is the necessity to continuously adapt them to the ongoing variations in the classifications of the different pathological variables included. This aspect is particularly relevant in the definition of the pathological extension of the primary tumor. Almost all available mathematical models use the 1997 version of the TNM staging system that is very similar to the more recent 2002 version [32]. Nevertheless, it is possible to hypothesize that the forthcoming TNM version will satisfy some of the proposals for reclassification of organ-confined (T1–2), locally advanced (T3–4), and lymph node involving (N1–2) tumors published in the last years [33–36].

Most of the mathematical models included in this revision are only validated for patients receiving a surgical treatment. The model proposed by Motzer et al. [10] is the only one that can be used to stratify metastatic patients who do not undergo radical nephrectomy. Hence, this model is very useful in the design and interpretation of phase II and III RCTs evaluating immunotherapeutic, chemotherapeutic and antiangiogenetic drugs available for medical therapy of advanced tumors.

Conclusion

Mathematical models have a prognostic accuracy higher than the one of the single clinical and/or pathological variables. The choice of the mathematical model to be used has to be pondered according to the clinical or research needs.

Integrated systems or algorithms, which are able to classify patients in groups with different prognoses, have to be preferred in follow-up planning and in the design and interpretation of the results of RCTs. In this setting, the most accurate one for conventional RCC is the SSIGN score, proposed by the Mayo Clinic group. Otherwise, the UISS allows the stratification of patients regardless of tumor histotype. The UISS is probably more adequate in the case of metastatic disease at the time of diagnosis.

On the other hand, nomograms are more useful in clinical practice, as they precisely estimate the DFS for each patient and allow a correct postoperative counseling of patients undergoing radical nephrectomy for RCC. The Sorbellini nomogram is the most suitable to be used in patients with conventional RCC [16]. The Kattan nomogram [6] might have more limited applications in patients with papillary or chromophobe RCC. The Karakiewicz nomogram [17] seems to have a very high prognostic accuracy in all RCC subtypes. The prognostic outcome of metastatic patients undergoing radical nephrectomy and IL-2 immunotherapy is best predicted by the model proposed by Leibovich et al. [13]. The model described by Motzer et al. [10] in 2002 is the only one able to stratify patients with metastatic RCC not eligible for surgical debulking in risk classes with different survival. The model by Kim et al. [14] is the only one including molecular markers, which might provide accurate prognostic information in this setting.

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