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A POSTOPERATIVE PROGNOSTIC NOMOGRAM PREDICTING RECURRENCE FOR PATIENTS WITH CONVENTIONAL CLEAR CELL RENAL CELL CARCINOMA

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ABSTRACT

Purpose: Few published studies have simultaneously analyzed multiple prognostic factors to predict recurrence after surgery for conventional clear cell renal cortical carcinomas. We developed and performed external validation of a postoperative nomogram for this purpose. We used a prospectively updated database of more than 1,400 patients treated at a single institution.

Materials and Methods: From January 1989 to August 2002, 833 nephrectomies (partial and radical) for renal cell carcinoma of conventional clear cell histology performed at Memorial Sloan-Kettering Cancer Center were reviewed from the center's kidney database. Patients with von Hippel-Lindau disease or familial syndromes, as well as patients presenting with synchronous bilateral renal masses, or distant metastases or metastatic regional lymph nodes before or at surgery were excluded from study. We modeled clinicopathological data and disease followup for 701 patients with conventional clear cell renal cell carcinoma. Prognostic variables for the nomogram included pathological stage, Fuhrman grade, tumor size, necrosis, vascular invasion and clinical presentation (ie incidental asymptomatic, locally symptomatic or systemically symptomatic).

Results: Disease recurrence was noted in 72 of 701 patients. Those patients without evidence of disease had a median and maximum followup of 32 and 120 months, respectively. The 5-year probability of freedom from recurrence for the patient cohort was 80.9% (95% confidence interval 75.7% to 85.1%). A nomogram was designed based on a Cox proportional hazards regression model. Following external validation predictions by the nomogram appeared accurate and discriminating, and the concordance index was 0.82.

Conclusions: A nomogram has been developed that can be used to predict the 5-year probability of freedom from recurrence for patients with conventional clear cell renal cell carcinoma. This nomogram may be useful for patient counseling, clinical trial design and effective patient followup strategies.

KEY WORDS: carcinoma, renal cell; prognosis, proportional hazards models

In the United States kidney tumors account for approximately 3% of malignancies, with approximately 32,000 new cases per year and 12,000 deaths from disease expected in 2004.[1] Renal cell carcinoma (RCC) accounts for 90% of all neoplasms found in the renal cortex. RCC does not constitute a single biological entity but rather a diverse group of malignancies.[2] Conventional clear cell renal cortical neoplasms (CCRCC) represent more than 65% of all RCC and are the most virulent of the subtypes. The remaining 35% of RCC subtypes are generally indolent (ie chromophobe and papillary RCC) or benign in nature (oncocytoma).[2] Currently, to our knowledge there are no effective radiographic methods to predict the histological subtype of RCC reliably before surgical resection. Accurate prediction of outcome and prognosis after surgical resection would be valuable for adjuvant trial design, counseling, effectively scheduling followup visits and imaging studies. In 2001 we published a postoperative nomogram designed to predict long-term freedom from recurrence after resection of RCC.[3] The malignant behavior of CCRCC led us to produce a new postoperative nomogram focused on this variant only.

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MATERIALS AND METHODS

Patients. From January 1989 to August 2002, 833 nephrectomies revealing CCRCC were performed at Memorial Sloan-Kettering Cancer Center (MSKCC).[4] After institutional review board approval these cases were reviewed from the MSKCC kidney database. Patients with von Hippel-Lindau disease (6), hereditary papillary RCC (2) as well as patients presenting with bilateral renal masses (23) were excluded from study because they would require separate modeling assumptions for accurate prognostic predictions. Patients in whom disease developed postoperatively in the other kidney were retained as part of the study cohort and, for the purposes of this study, were considered recurrences at the time of this new disease development. The Heidelberg classification of renal cortical neoplasms was used.[4] Cases of stage pT4 (9) and pT3c (2) were excluded from the cohort due to small frequencies. Patients with distant metastases (54) or metastatic regional lymph nodes (21) before or at the time of operation were excluded from the study, as were 8 patients who underwent nephrectomy elsewhere and 7 patients whose data were lost in audit. The remaining 701 patients eligible for the study had undergone single nephrectomy, either radical or partial, for unilateral locally confined disease.

The end points of our study were time until detection of

kidney cancer recurrence and time to last followup if the patient was alive, or time until death if the patient was deceased. New cancer may have developed due to local or metastatic recurrence, or contralateral disease at any time after surgery, or death from kidney cancer, whichever occurred first. Recurrence was defined as the development of a new tumor in a patient after nephrectomy, and type of recurrence was ignored.

The literature was reviewed for prognostic variable selection. Clinicopathological factors used included pathological stage, Fuhrman grade, tumor size, necrosis, vascular invasion and clinical presentation. Incidental lesions were defined as tumors detected during evaluation of an unrelated medical condition or during followup for an unrelated cancer. Locally symptomatic lesions were those detected after evaluation of hematuria, flank pain, or flank or abdominal mass. Systemically symptomatic lesions included those detected upon evaluation of signs and symptoms caused by paraneoplastic disorders or systemic symptoms (ie fever, weight loss, extreme fatigue) that led to the discovery of tumor.

Since prior studies have shown no significant difference in survival after treatment with nephron sparing surgery versus radical nephrectomy for tumors 4 cm or smaller,[5,6] procedure type was not included in our analysis. Pathology slides were reviewed by pathologists at MSKCC and Columbia University depending on the site of slide origin. The 2002 staging system of the American Joint Committee on Cancer was used.[7]

Statistical analysis. Progression-free probability was estimated using the Kaplan-Meier method. Multivariate analysis was performed with Cox proportional hazards regression. A nomogram was constructed for freedom from recurrence with the information obtained from the Cox proportional hazards regression model. To avoid forcing continuous variables such as size to behave as linear variables we used restricted cubic splines. We also used splines for Fuhrman grade since it was analyzed as an ordered variable.

Model validation was performed with 200 cases from the urological oncology database of the Department of Urology at Columbia University (table 1). Equal exclusion criteria were applied to the validation cases. All simulations and analyses were conducted with S-Plus software Version 2000 Professional Edition with the Design library (Mathsoft Data Analysis Products Division, Seattle, Washington).

TABLE 1. *Descriptive statistics for study and validation cases with CCRCC*

	MSKCC		Columbia University	
No. cases	701		200	
No. presentation type (%):				
Incidental	488	(69.61)	113	(56.5)
Locally symptomatic	178	(25.40)	77	(38.5)
Systemically symptomatic	32	(4.56)	10	(5)
Not available	3	(0.43)	0	
Pathological tumor size (cm):				
Min	0.5		0.7	
Median	4.5		4.3	
Mean	5.29		5.1	
Max	21		18	
Not available	0		2	
No. 2002 UICC stage (%):				
pT1a	281	(40.09)	76	(38)
pT1b	163	(23.25)	34	(17)
pT2	58	(8.27)	10	(5)
pT3a	130	(18.54)	42	(21)
pT3b	68	(9.70)	38	(19)
Not available	1	(0.14)	0	
No. Fuhrman grade (%):				
I	66	(9.42)	32	(16)
II	397	(56.63)	113	(56.5)
III	139	(19.80)	42	(21)
IV	25	(3.57)	13	(6.5)
Not available	74	(10.56)	0	
No. tumor necrosis (%)	23	(3.28)	24	(12)
No. microvascular invasion (%)	33	(4.71)	81	(40.5)

RESULTS

Descriptive clinicopathological statistics for the study and validation cohorts are depicted in table 1. There were 281 (40.1%) patients in the study cohort (MSKCC) with stage pT1a, 163 (23.3%) with pT1b, 58 (8.3%) with pT2, 130 (18.5%) with pT3a and 68 (9.7%) with pT3b. A total of 66 (9.4%) patients had Fuhrman grade I, 397 (56.6%) Fuhrman grade II, 139 (19.8%) Fuhrman grade III and 25 (3.6%) Fuhrman grade IV. The smallest lesion was 0.5 cm in maximum diameter and the largest 21 cm, with a median size of 4.5 cm and a mean size of 5.3 cm. The presence of tumor necrosis was reported in 23 (3.3%) cases (not available in 7 cases) and microvascular invasion in 33 (4.7%) cases (not available in 10 cases). There were 488 (70%) patients presenting with incidentally detected tumors, 178 (25.4%) with locally symptomatic tumors and 32 (4.6%) with systemically symptomatic tumors. Three patients had not been assigned a clinical presentation and 1 patient did not have a pathological stage.

There were 76 (38%) patients in the validation cohort (Columbia University) with stage pT1a, 34 (17%) with pT1b, 10 (5%) with pT2, 42 (21%) with pT3a and 38 (19%) with pT3b. A total of 32 (16%) patients had Fuhrman grade I, 113 (56.5%) Fuhrman grade II, 42 (21%) Fuhrman grade III and 13 (6.5%) Fuhrman grade IV. The smallest lesion was 0.7 cm in maximum diameter and the largest 18 cm, with a median size of 4.3 cm and a mean size of 5.1 cm. Tumor size was not available in 2 cases. Tumor necrosis was reported in 24 (12%) cases and microvascular invasion in 81 (40.5%) cases (presence or absence of tumor necrosis and microvascular invasion was determined for all cases). There were 113 (56.5%) patients presenting with incidentally detected tumors, 77 (38.5%) with locally symptomatic tumors and 10 (5%) with systemically symptomatic tumors.

Disease recurrence was noted in 72 patients of the study cohort. Median and maximum followup for the MSKCC cohort was 33 and 120 months, respectively. Those without evidence of disease had a median and maximum followup of 31 and 120 months, respectively. Of the 200 validation cases disease recurrence was noted in 26. Median and maximum followup for the Columbia University cohort was 33 and 149 months, respectively. Those without evidence of disease had a median and maximum followup of 31 and 149 months, respectively. The 5-year freedom from recurrence probability for the study cohort was 80.9% (95% CI 75.7% to 85.1%).

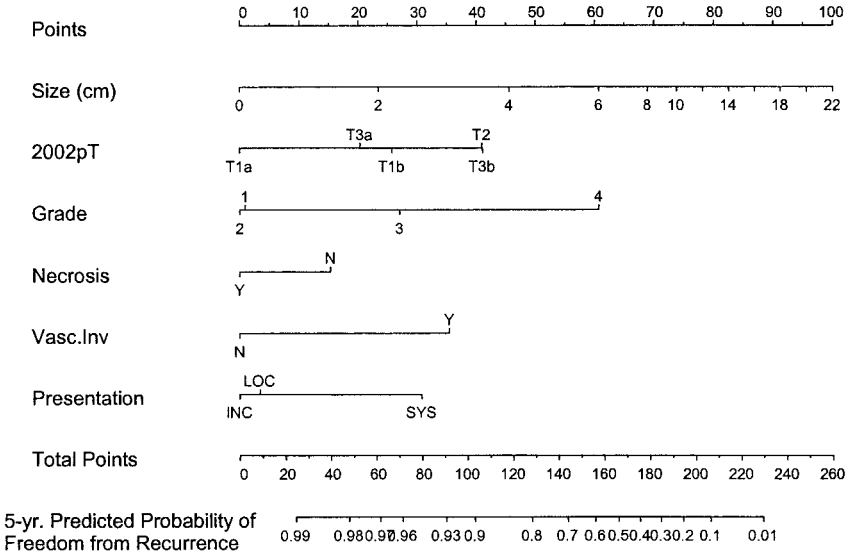
Only microvascular invasion ($p = 0.012$) and Fuhrman grade ($p = 0.002$) were associated with freedom from recurrence in multivariate analysis (table 2). Nevertheless, all variables were used in nomogram modeling. A nomogram was generated from the Cox regression model (see figure). In external validation the concordance index for the nomogram was found to be 0.82.

DISCUSSION

Renal cell carcinoma accounts for 90% of neoplasms found in the renal cortex. RCC does not constitute a single biological entity but a diversity of malignancies with different natural histories, etiologies and histologies.[2] The general characteris-

TABLE 2. *Multivariate analysis*

	p Value
Tumor size	0.087
2002 UICC stage	0.289
Fuhrman grade	0.002
Necrosis	0.441
Microvascular invasion	0.012
Clinical presentation	0.065



Indications for Physician: Locate the patient's tumor size on the Size axis. Draw a line upwards to the Points axis to determine how many points towards recurrence the patient receives for his symptoms. Repeat this process for the other axes, each time drawing straight upward to the Point axis. Sum the points achieved for each predictor and locate this sum on the Total Points axis. Draw a straight line down to find the patient's probability of remaining recurrence free for 5 years assuming he or she does not die of another cause first.

Instruction to the Patient: "Mr. X, if we had 100 men or women exactly like you, we would expect (predicted percentage from nomogram) to remain free of their disease 5 years following surgery, though recurrence after 5 years is still possible".

Freedom from recurrence nomogram. Vasc. Inv, microvascular invasion. INC, incidental presentation. LOC, locally symptomatic presentation (flank pain, flank or abdominal mass, hematuria). SYS, systemic symptoms due to metastatic disease.

tics of RCC subtypes are described in the Heidelberg classification of renal cortical tumors.[4] Conventional clear cell renal cortical neoplasms represent approximately 65% of RCC and posses the greatest malignant potential of all RCC subtypes. The remaining 35% of RCC subtypes are indolent or benign in nature.[2] Unfortunately the only way to know the histological subtype of RCC at present is through pathological analysis.

Accurate prediction after surgical resection of a renal cortical neoplasm would be valuable for counseling, scheduling followup visits and their intensity, and identifying poor risk patients who could benefit from enrollment in adjuvant therapy protocols. Since 90% of patients with renal cortical tumors in whom metastatic disease has developed have the conventional clear cell histological variant,[8] we decided to produce a nomogram focused on specific cytological and clinical aspects of CCRCC (see figure).

Nomograms consist of graphic depictions of prediction models.[3,9,10] One of the most appealing properties of these tools is the ability to account for multiple prognostic factors simultaneously. Nomograms make unbiased predictions based on objective data, and provide a prognosis which is useful in clinical care and research. Furthermore, nomogram calculations are simple to perform with free software available for personal digital assistants or on Internet sites (www.nomograms.org).

In 2001 we published the first nomogram intended to predict freedom from recurrence after surgery for patients with localized RCC.[3] Because of the different metastatic potentials of the histological subtypes of RCC, not all known prognostic factors could be used in the common model. Some factors such as Fuhrman grade,[11] which are of known prognostic significance for CCRCC but not for the chromophobe variant,[2] had to be omitted, rendering the predictive ability of that nomogram somewhat weaker. The area under the receiver operating curve (ROC) for the initial nomogram was 0.74. Recent data show that tumor histology is one of the most important prognostic factors for patients with RCC.[2,3,12,13] Thus, we created a new nomogram focusing on the CCRCC variant which incorporated the latest published data regarding the most significant and widely available clinicopathological features for the accurate prediction of the probability of freedom from recurrence after nephrectomy. Accordingly TNM stage, size, Fuhrman grade, presence of necrosis, microvascular invasion and clinical presentation (ie incidental asymptomatic, or locally symptomatic or systemically symptomatic) were included in our predictive model.

Of the previously mentioned variables only microvascular invasion ($p = 0.012$) and Fuhrman grade ($p = 0.002$) were associated with freedom from recurrence (table 2). Variables not found to be statistically significant in multivariate analysis were nevertheless included in our final nomogram. The latter is routinely done for complex mathematical modeling since procedures which exclude statistically insignificant variables have been reported to decrease the predictive accuracy of those models by exaggerating the effects of the remaining variables.[3]

A large body of evidence suggests that Fuhrman grade is one of the most ominous prognostic factors for CCRCC survival.[2,13,14] This was confirmed in our study in which Fuhrman grade was found to be associated with freedom from recurrence ($p = 0.002$). Furthermore, as seen in the figure, we concur with previous studies which show that the higher the grade, the worse the prognosis for freedom from recurrence.

As reported in the literature our nomogram shows that as

tumor size increases freedom from recurrence decreases.[15–17] However, in this study tumor size only approached statistical significance ($p = 0.087$). It is interesting to note that tumor size partly defines pathological stage, namely pT1a (less than 4 cm), pT1b (greater than 4 and less than 7 cm) and pT2 (greater than 7 cm). However, pathological stage was not found to be statistically significant in this nomogram and the pathological stage axis was found to be minimal in size compared to the size axis of the nomogram. This seems to confirm previously reported findings regarding the importance of tumor size by itself as a significant prognostic variable for CCRCC, independent of pathological stage.[16, 17] It is further demonstrated by nomogram depictions of pathological stage which show no clear-cut trend in the pathological stage axis contrary to expectations (ie that tumors in cases with higher pathological stages recur more frequently than lower pathological stages). The latter situation may be explained by the fact that small tumors may be of high pathological stage due to fat or renal vein extension (pT3a), or inferior vena cava invasion (pT3b and pT3c), but this does not necessarily decrease patient survival. These findings seem to demonstrate that the prognostic relevance of pathological stage can be markedly decreased by the presence or absence of other prognostic factors.

Clinical presentation, akin to performance status, was recently shown to be of importance as a prognosticator in RCC. Lee et al demonstrated that patients with asymptomatic incidentally detected tumors tended to do better after nephrectomy than those presenting with locally symptomatic tumors, who in turn did better than those presenting with systemically symptomatic tumors.[15] Our data concur with the previously mentioned results which can be seen by the placement of each clinical group in the presentation axis of the nomogram.

The nomogram in our study shows that the presence of tumor microvascular invasion indicates a worse prognosis for freedom from recurrence ($p = 0.012$). This may be related to the fact that microvascular invasion and angiogenesis may be more important during the early stages of tumorigenesis than later in the course of the disease.[18] Several authors have shown that the presence of tumor necrosis is indicative of more aggressive and virulent tumor behavior.[17] However, in this study the absence of necrosis was found to be associated with a worse outcome for freedom from recurrence, although this finding was not statistically significant ($p = 0.44$).

As opposed to most predictive models for renal cell carcinoma, the nomogram presented in this study has been validated with extramural data. A total of 200 cases from Columbia University Medical Center were used for this purpose (table 1). As can be seen in table 1 there are differences between the sets of data which are a reflection of the somewhat different patient populations treated at each institution and of the fact that physicians at both centers may come to slightly different conclusions when presented with a particular case. Therefore, external validation makes the results of the current study more powerful because it makes this model a nonpathologist, noninstitution specific device, and makes the predictive ability of the nomogram more potentially useful for clinicians from other medical centers.

The current nomogram has from several weaknesses. This nomogram predicts recurrence to a maximum of 5 years. It is possible that patients may experience disease recurrence, or metastasis or death after 5 years since renal cell carcinoma has a long natural history and late relapses are not rare. A technical limitation of the current nomogram is that it uses a point value system. An alternative to this representation would be a table or survival curves. However, tables and curves require the categorization of continuous variables such as tumor size, which would reduce the predictive accuracy of the model. Finally, one of the most important limitations of the present study is that it is not 100% accurate. Nevertheless, accuracy appears improved compared to that of the 2001 model[3] as attested by the increment in the ROC for this nomogram (0.82) compared to the prior model (0.74).

CONCLUSIONS

We present a postoperative nomogram focusing on the conventional clear cell histology of RCC that incorporates clinical and histological parameters. The predictive value as defined by the concordance index is 0.82. This nomogram will serve as a valuable tool in research and clinical practice. We plan to add this model to our free software at www.nomograms.org.

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