Prognostic Nomogram for Renal Insufficiency After Radical or Partial Nephrectomy

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Purpose: We analyzed prognostic factors to predict renal insufficiency after partial or radical nephrectomy. We developed and performed internal validations of a postoperative nomogram for this purpose. We used a prospectively updated renal tumor database of more than 1,500 patients.

Materials and Methods: From July 1989 to October 2003, 161 partial nephrectomies and 857 radical nephrectomies performed at Memorial Sloan-Kettering Cancer Center for renal cortical tumors were analyzed. Computerized tomography images were reviewed by a single radiologist. Kidney volume was calculated using the ellipsoid formula, $V = L1 \times L2 \times L3 \times \pi/6$, where V represents volume and L represents length. Renal insufficiency was defined by 2 serum creatinine values greater than 2.0 mg/dl at least 1 month postoperatively. Tumor histology was not an exclusion criterion and yet we excluded cases of bilateral synchronous disease. Prognostic variables were preoperative serum creatinine, American Society of Anesthesiologists score, percent change in kidney volume after surgery, and patient age and sex.

Results: Renal insufficiency was noted in 105 of the 857 patients with radical nephrectomy (12.3%) and in 6 of the 161 with partial nephrectomy (3.7%) studied. Patients had a median followup of 21.2 months (maximum 157.9). The 7-year probability of freedom from renal insufficiency in the cohort was 79.1% (95% CI 74.6 to 83.6). The nomogram was designed based on a Cox proportional hazards regression model. Following internal statistical validation nomogram predictions appeared accurate and discriminating with a concordance index of 0.835.

Conclusions: A nomogram was developed that can predict the 7-year probability of renal insufficiency in patients undergoing radical or partial nephrectomy.

Key Words: kidney, nephrectomy, nomograms, prognosis

Renal cell carcinoma represents approximately 3% of malignancies with approximately 32,000 new cases and 12,000 deaths expected in the United States in 2004.[1] In recent years our understanding of the biology of RCC has changed. RCC is no longer considered a single biological entity but a family of neoplasms, referred to as RCTs, with different histological features, cytogenetic defects and metastatic potential. In addition, the natural history of the disease seems to have evolved during the years with RCTs now being discovered most often incidentally with lower pathological stage and smaller size at diagnosis than has been previously observed,[2] leading to wide acceptance of kidney sparing surgical approaches for T1 tumors.[3] Furthermore, contemporary data from the Mayo Clinic and MSKCC have demonstrated that in the long term the risk of renal insufficiency in patients who have undergone radical nephrectomy for a T1a tumor is higher than the risk in similar patients who have undergone partial nephrectomy, although the 2 groups of patients experience similar oncological benefits and overall survival.[4,5]

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With this in mind we created a nomogram for accurately predicting renal insufficiency in patients undergoing partial or radical nephrectomy. This nomogram is useful for patient counseling, clinical trial design and creating effective patient followup strategies.

MATERIALS AND METHODS

From July 1989 to October 2003, 1,623 nephrectomies for RCT performed at MSKCC were reviewed from the Department of Urology prospectively updated renal tumor database. Appropriate Institutional Review Board approval was obtained for this study. All patients who underwent partial or radical nephrectomy were included in the study cohort regardless of tumor histology. If patients underwent nephrectomy before arrival at MSKCC, only nephrectomy performed at MSKCC was considered. All subsequent nephrectomies were also disregarded for study purposes. A review of the literature was performed to determine the prognostic variables to be used in the study, including preoperative serum creatinine, ASA score, percent change in kidney volume after surgery, and patient age and sex.

Kidney volume was calculated using the ellipsoid formula, $V = L1 \times L2 \times L3 \times \pi/6$,[6] where V represents volume and L represents length. Only measurements from CT were used. The percent change in kidney volume after surgery

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TABLE 1. *Descriptive statistics*

	Partial Nephrectomy	Radical Nephrectomy	Totals	*p* Value
No. pts (%)	161 (15.8)	857 (84.2)	1,018	
Pathological tumor size (cm):				<0.001
Mean	3.0	6.8	6.2	
Median	2.6	6.0	5.5	
Minimum	0.8	1.0	0.8	
Max	10.0	21.0	21.0	
Sex:				0.474
M	104 (64.6)	528 (61.6)	632 (62.1)	
F	57 (35.4)	329 (38.4)	386 (37.9)	
Age:				0.001
Mean	58.7	62.5	61.9	
Median	61.4	63.8	63.4	
Minimum	22.4	14.7	14.7	
Max	82.6	91.3	91.3	
ASA score:				0.394
0–1	12 (7.5)	71 (8.3)	83 (8.2)	
2	100 (62.1)	475 (55.4)	575 (56.5)	
3–4	49 (30.4)	311 (36.3)	360 (35.4)	
% Kidney vol change:				<0.001
Mean	18.0	100	87.03	
Median	20.2	100	100	
Minimum	−95.7	100	−96	
Max	85.5	100	100	
Preop serum creatinine (mg/dl):				0.135
Mean	1.03	1.1	1.1	
Median	1.0	1.1	1.0	
Minimum	0.5	0.5	0.5	
Max	1.9	8.3	8.3	
No. postop renal insufficiency (%)	6 (3.7)	105 (12.3)	111 (10.9)	0.005

was defined using the formula, $(V1 - V2) \times 100\%/V1$, where V2 represents postoperative volume calculated from postoperative CT and V1 represents preoperative volume calculated from preoperative CT. CT images used for preoperative volume calculation were those done before surgery closest in time to the actual surgical date. CT images used for postoperative volume calculation were those done closest in time to the date marking postoperative month 6. CT studies were reviewed by a single radiologist at MSKCC. A total of 262 patients without preoperative and postoperative CT images, or with preoperative CT studies older than 6 months, or those done less than 4 or more than 24 months postoperatively were excluded from study.

Patients with synchronous bilateral renal masses at diagnosis (49) as well as those with procedures done elsewhere (45), familial disease (7), missing ASA scores (252), missing postoperative creatinine values (7) and missing preoperative creatinine values (1) were excluded from analysis. Eight cases lost in audit were excluded from analysis.

Renal insufficiency was defined by 2 serum creatinine values more than 2 mg/dl,[7,8] of which the first was observed at least 1 month postoperatively. Patients were not excluded from study because of increased preoperative creatinine.

The study end points were time to the detection of renal insufficiency and time to last followup. Time to renal insufficiency from nephrectomy was achieved when the first creatinine of more than 2 mg/dl was observed.

We modeled clinical data on 161 partial nephrectomies and 857 radical nephrectomies. Freedom from renal insufficiency was estimated using the Kaplan-Meier method. Multivariate analysis was done with Cox proportional hazards regression. A nomogram was created based on the Cox proportional hazards regression model. Bootstrapping was used to internally validate the nomogram.[9] Simulations and analyses were performed with S-Plus®, version 2000 Professional Edition with the Design library (Mathsoft®).

RESULTS

Table 1 lists study descriptive clinical statistics. In the study cohort 857 patients (84.18%) underwent radical nephrectomy and 161 (15.81%) underwent partial nephrectomy. Sex distribution was 632 male patients (62.1%) and 386 female patients (37.9%). The youngest patient was 14.7 years old and the oldest was 91.3 years old (mean 61.9, median 63.4). ASA score was 0 or 1, 2 and 3 or 4 in 83 (8.2%), 575 (56.5%) and 360 patients (35.4%), respectively. The mean percent change in kidney volume postoperatively was 87.03% (median 100%, minimum −96% and maximum 100%). Mean preoperative serum creatinine was 1.1 mg/dl (median 1.0, minimum 0.5 and maximum 8.3). In 15 cases (1.5%) preoperative creatinine was more than 2 mg/dl, including 8 (7.2% of the total number with renal failure postoperatively) that fit the definition of renal insufficiency postoperatively, while 7 did not. Mean followup in the study cohort was 31.6 months (median 21.2, minimum 0.1 and maximum 157.9).

A total of 111 patients (10.9%) experienced renal insufficiency, of whom 105 (12.3%) underwent radical nephrectomy and 6 (3.7%) underwent partial nephrectomy. Median time from partial or radical nephrectomy to renal insufficiency was 14.4 months.

On multivariate analysis all prognostic variables except ASA score ($p = 0.5582$) were found to be associated with freedom from renal insufficiency after nephrectomy, including age ($p = 0.0001$), sex ($p = 0.0031$), preoperative creatinine ($p = 0.0001$) and percent change in kidney volume after surgery ($p = 0.0179$, table 2). Nevertheless, all variables were used for nomogram modeling since excluding insignificant variables would have over stated the effects of the remaining variables, thus, decreasing the predictive accuracy of the model.

A nomogram was generated from the Cox regression model (fig. 1). After bootstrapping the concordance index for

TABLE 2. *Multivariate analysis*

	p Value
Age	0.0001
Sex	0.0031
ASA score	0.5582
Preop creatinine	0.0001
% Kidney vol change	0.0179

the nomogram was found to be 0.835. Calibration appeared to be good (fig. 2).

DISCUSSION

For decades after the article of Robson in the 1960s[10] radical nephrectomy was considered the gold standard for RCC. Historically proponents of radical nephrectomy as the single treatment modality for RCC have invoked studies based on kidney donation, in which patients did well after excision of a single kidney. The caveat in those studies is that the patient population conforming donor nephrectomy cohorts tend not to match the characteristics in patients undergoing nephrectomy due to RCC. Donor patients tend to be young (median age 40 years[11]) and healthy, without significant comorbidities. On the other hand, patients with RCC are older (average age mid seventh decade of life) and they may have significant comorbidities, such as hypertension, obesity and diabetes mellitus.[12]

Interestingly the incidence of ESRD has increased steadily in the United States in the last 2 decades from less than 100 per million new cases in 1980 to 333 per million in 2002. By 2030 it is estimated that more than 2 million Americans will require dialysis or a renal transplant.[13] Although the cause of this increase in ESRD has not been found, increased blood pressure, diabetes mellitus, tobacco smoking and increasing age are known risk factors.[14] Most importantly recent data show that the risk of cardiovascular morbidity and mortality increases not only in patients with ESRD, but also in those with decrements in renal function even before they experience renal failure.[15]

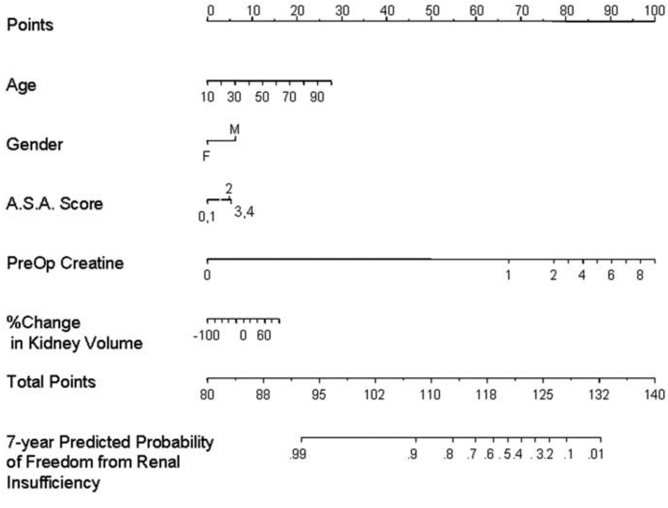

FIG. 1. Renal failure nomogram predicting freedom from renal Insufficiency in patients after partial or radical nephrectomy. Indications for physician are to locate patient age on age axis. Draw line upward to points axis to determine how many points toward recurrence patient receives for age. Repeat this process for other axes, each time drawing straight upward to point axis. Sum points achieved for each predictor and locate this sum on total points axis. Draw straight line down to find patient probability of remaining free from renal insufficiency for 7 years. Instruction to patient is, "Mr. X, if we had 100 men or women exactly like you, we would expect (predicted percent from nomogram) not to develop renal insufficiency 7 years following surgery, although renal insufficiency after 7 years is still possible."

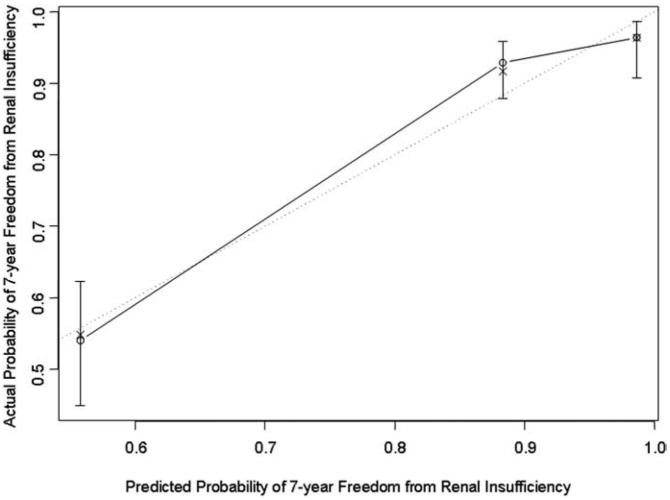

FIG. 2. Calibration of nomogram for renal insufficiency after nephrectomy. In general it appeared that nomogram predictions were accurate to within 10% of actual freedom from renal insufficiency after partial or radical nephrectomy. Horizontal axis represents nomogram prediction of probability of renal insufficiency not developing. Vertical axis represents actual freedom from renal insufficiency estimated at 7 years with Kaplan-Meier method. Broken line indicates reference line on which ideal nomogram would lie. Solid line indicates current nomogram performance. Circles represent subcohorts of our data set. X indicates bootstrap corrected estimate of nomogram performance with repeat samples. Vertical bars represent 95% CI.

At the same time our understanding of RCC has changed in recent years. We now know that RCC is not a single entity but a family of tumors, of which each has a different biology and metastatic potential with 35% of RCTs having indolent or benign clinical behavior. In addition, since the early 1980s, we have observed a stage and size migration of RCC with neoplasms now being discovered at early stages, incidentally and at smaller sizes than previously observed.[2] Evidence has emerged supporting partial nephrectomy as an equivalent means of achieving oncological benefits similar to those of radical nephrectomy for T1 tumors.[3,16,17] Furthermore, contemporary data from the Mayo Clinic and MSKCC have shown that in the long term patients undergoing radical nephrectomy for T1a tumors are at higher risk for renal insufficiency than patients undergoing partial nephrectomy.[4,5]

In light of the current strong increase in chronic kidney disease in the United States, concomitant efforts by the medical community to prevent deterioration in renal function in patients and considering the new evidence regarding treatment options for RCC we created a nomogram that would accurately predict the probability of remaining free from renal insufficiency after partial or radical nephrectomy. Accurate prediction of renal insufficiency in patients undergoing nephrectomy would be valuable for patient counseling concerning therapeutic modalities preoperative and postoperatively. Prognostic variables used in our model were patient age, sex, ASA score, serum preoperative creatinine and percent change in kidney volume after nephrectomy.

Of the mentioned variables only ASA score, which is a proxy for patient comorbidities,[18] was not found to be statistically significant ($p = 0.5582$). Nevertheless, all prognostic variables were included in our nomogram model since it has been shown that excluding statistically insignificant variables tends to overemphasize the remaining variables, decreasing the predictive accuracy of the model.[9]

This study shows that the higher the ASA score and, thus, the number of comorbidities in a particular patient, the more likely the patient is to experience renal insufficiency (fig. 1). This concurs with recent data from Ito et al showing that comorbidities such as hypertension and diabetes are associated with an increased risk of renal failure following unilateral radical nephrectomy.[19] Furthermore, data from the Framingham Heart Study show that 20% of patients with increased serum creatinine have cardiovascular disease, more than 30% are hypertensive and 10% are diabetic.[8]

It was not a surprise to find that age was associated with renal insufficiency ($p = 0.0001$). It has been demonstrated that, as patients age, nephrons become atrophied and the glomerular filtration rate decreases.[20] Culleton et al found that men were at 21% increased risk for high serum creatinine when they increased in age from 60 to 70 years.[8] In women they documented a 66% increase in the risk of hypercreatinemia for every 10-year increase in age. Furthermore, data from the United States Renal Data System show that 35% of patients with ESRD are in the 45 to 64-year-old age group and a further 25% are older than 75 years.[13] Our results concur with the latter reports by indicating a higher risk of renal insufficiency in older patients. This is important considering that the average age at presentation in patients with renal cortical tumors is 64 years.

As shown in the nomogram, men were found to have a higher probability of renal insufficiency than women ($p = 0.0031$). These results concur with data from the United States Renal Data System database showing higher ESRD incidence rates in males than in females (409 male patients per million population with ESRD compared to 276 females per million population).[13]

In this study we did not exclude patients because of preoperative serum creatinine higher than 2 mg/dl. As reported, 15 patients had serum creatinine more than 2 mg/dl before surgery. Interestingly only 8 patients (7.2% of the total number with renal insufficiency) remained with high creatinine postoperatively and they were considered to have renal insufficiency under the current study definitions. In addition, our study shows that the level of preoperative serum creatinine is associated with freedom from renal insufficiency ($p = 0.0001$). Consequently, as depicted in the nomogram, the higher the preoperative creatinine value, the higher the risk of renal insufficiency. The latter supports recent data from Ito et al, in whose study preoperative creatinine was found to be an independent predictor of renal insufficiency after radical nephrectomy.[19]

We mindfully devised this nomogram to include factual measurements of kidney volume and not simply volumes calculated from pathological specimen size. We did this to consider changes that occur to the kidney postoperatively that are part of its normal healing process and may affect its function. It has previously been suggested that 50% of kidney volume must remain viable to preserve renal function. The studies of Lau[4] and McKiernan[5] et al seem to demonstrate that preserving renal mass during a surgical procedure tends to decrease the risk of renal insufficiency in patients. Our results concur with the results of these studies. The percent change in kidney volume was found to be associated with freedom from renal insufficiency but, as can be seen from the percent change in kidney volume axis, we also found that the higher the change in volume, ie the larger the renal mass being excised, the higher the risk of renal insufficiency.

The nomogram in this study has from several limitations. 1) It predicts freedom from renal insufficiency to a maximum of 7 years. It is possible that some patients have renal insufficiency after 7 years and that event would escape the predictive value of this nomogram. 2) Renal insufficiency was defined in this study as a serum creatinine of more than 2 mg/dl twice postoperatively. The literature is vague when defining renal insufficiency. Nevertheless, we used a stricter definition than well designed studies, such as the Framingham Heart Study[8] and National Health and Nutrition Examination Survey III,[7] in which renal insufficiency was defined as a serum creatinine of greater than 1.5 and 2 mg/dl, respectively. 3) Another weakness in this study was the use of the ellipsoid formula to calculate renal volumes. It is evident that the use of any geometric formula to describe the volume contained in a kidney is inaccurate, especially after surgical resection and renal parenchymal reconstruction. Nevertheless, in the absence of 3-dimensional CT in all our patients it was decided that using the ellipsoid shape to describe the shape of a kidney was a better fit than using other geometric forms. 4) Nomogram results were validated through bootstrapping. A more accurate method to validate our results could have been the use of external data. 5) This nomogram is not 100% accurate and yet its accuracy seems most impressive, judging by its concordance index of 0.835.

CONCLUSIONS

To our knowledge we present the first prediction model for freedom from renal insufficiency in patients undergoing partial or radical nephrectomy. It incorporates readily available clinical parameters. As defined by the concordance index, its predictive value is 0.835. This nomogram will be useful for patient counseling, clinical trial design and creating effective patient followup strategies.

Abbreviations and Acronyms

ASA	=	American Society of Anesthesiologists
CT	=	computerized tomography
ESRD	=	end stage renal disease
MSKCC	=	Memorial Sloan-Kettering Cancer Center
RCC	=	renal cell carcinoma
RCT	=	renal cortical tumor

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EDITORIAL COMMENT

Prognostic nomograms and other similar models to aid in clinical decision making have helped define previously vague patient care scenarios in many circumstances. Although this postoperative nomogram is applicable in all potential patients, the concept is better suited to patients making decisions before surgical therapy. With the cow out of the barn it is unclear how this nomogram benefits the patient, as opposed to cancer nomograms that can identify patients at high risk for potential adjuvant therapy.

Additionally, most clinicians attempt to identify patients who have risk factors for progressive renal deterioration, including hypertension, diabetes and more recently obesity. Instead, the authors use ASA score, a subjective value that was not recorded in 16% of the patient cohort, as a potential surrogate marker for these factors. Finally, the nomogram was developed in a highly selected referral patient cohort and it was not externally validated, thereby potentially decreasing its applicability in all patients. Future models that consider these factors will likely be an important tool for clinicians and patients.

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REPLY BY AUTHORS

Chronic kidney disease, whether due to medical or surgical causes alone or in combination, is a risk for death, cardiovascular events and hospitalization (reference 15 in article). During the last several years investigators from our center and elsewhere have raised the level of awareness regarding the deleterious impact of radical nephrectomy on the future renal health of patients. In earlier studies (references 4 and 5 in article) and our current study the serum creatinine value of 2 mg/dl is likely an underestimate of preoperative and postoperative renal insufficiency with 24-hour urinary collections or formulas incorporating age, gender and race available for more precise determinations. Our study clearly shows that an appreciation of the preoperative serum creatinine, the most important prognostic factor in our current nomogram as evidenced by its position, can have a key role in surgical planning and possibly prevent the casual radical nephrectomy for the small, good prognostic renal cortical tumor. Today, the urological surgeon needs to provide effective local tumor control and maintain a careful eye on the long-term renal health of the patient.