Preoperative Prognostic Nomogram (Probability Table) for Renal Cell Carcinoma Based on TNM Classification

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Abbreviations and Acronyms

CT = computerized tomography

RCC = renal cell carcinoma

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Purpose: Recently several prognostic nomograms have been developed to predict the prognosis of malignant diseases, including renal cell carcinoma. However, to our knowledge a preoperative prognostic nomogram that predicts survival in patients with renal cell carcinoma is not available. We developed a preoperative nomogram based on the TNM classification that predicts cause specific survival in patients with renal cell carcinoma.

Materials and Methods: A total of 545 patients with renal cell carcinoma, including metastatic disease, who underwent radical nephrectomy or nephron sparing surgery at our institution were included in the study. Cases were staged according to the 2002 UICC TNM system, 6th edition. T, N and M factors were used as prognostic factors and a Cox proportional hazards regression model was developed to predict cause specific survival. A nomogram to predict cause specific survival was developed by repeating the analysis on 200 bootstrap samples. To validate the nomogram a concordance index was estimated and calibration was also examined by plotting the predictions made by the nomogram.

Results: Overall 1, 3 and 5-year patient survival was 95.2%, 92.0% and 89.9%, respectively. T, N and M factors were significant prognostic factors in the Cox proportional hazards regression model. Using the combined TNM factors we developed a nomogram predicting 1, 3 and 5-year cause specific survival rates. The nomogram had excellent ability to discriminate, as evidenced by a concordance index of 0.81, and it was generally well calibrated.

Conclusions: The preoperative information shown by this nomogram may be important for obtaining informed consent from patients with renal cell carcinoma who have indications for surgery.

Key Words: kidney; nomograms; carcinoma, renal cell; mortality; prognosis

Recently several prognostic nomograms have been developed to predict the prognosis of diseases or treatment outcomes in urology. These nomograms have been used in clinical practice to determine the treatment strategy and obtain informed consent. Currently 7 RCC nomograms have been published that predict prognosis or metastasis. A group from Memorial Sloan-Kettering Cancer Center developed postoperative prognostic nomograms for locally confined RCC that predict the probability of freedom from recurrence for 5 or 7 years after surgery.[1–3] They recently presented a preoperative nomogram that predicts metastatic recurrence following nephrectomy.[4] Karakiewicz et al developed a postoperative nomogram to predict survival in patients with RCC[5] and Hutterer et al also devel-

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oped nomograms predicting a probability of nodal metastasis at nephrectomy or distant metastasis at diagnosis.[6,7]

Nephrectomy is now accepted as first line treatment for localized RCC. A recent study concluded that in patients with metastatic RCC nephrectomy also improved survival if patients presented with good performance status.[8] Therefore, a preoperative prediction of patient survival, including in those with metastatic RCC, may be helpful for physicians and patients discussing treatment or obtaining informed consent. Furthermore, survival is a most important indicator for assessing the clinical outcome in patients who undergo surgical treatment. However, to our knowledge a preoperative prognostic nomogram to predict cause specific survival in patients with RCC is not available.

The TNM classification is now widely accepted to provide significant prognostic factors in patients with RCC. A recent study also concluded that tumor classification using the TNM staging system is a significant predictor of cause specific survival in this patient cohort.[9] Furthermore, TNM classification can be estimated preoperatively using CT and x-ray, which is different than using postoperative factors such as histological typing or nuclear grading. We developed a preoperative prognostic nomogram based on the TNM classification to predict cause specific survival in patients, including those with metastatic RCC.

MATERIALS AND METHODS

From December 1985 to December 2003, 545 patients with RCC underwent radical nephrectomy or nephron sparing surgery at our institution. Cases were staged with CT of the abdomen and pelvis, chest CT or chest x-ray. Regional lymph node involvement or distant metastasis at diagnosis was not considered a contraindication to nephrectomy for improving survival and cytoreduction.[8,10] However, patients with poor performance status and advanced age or significant comorbidity affecting life expectancy were excluded from the indication for nephrectomy. Advanced disease was generally treated with interferon-α or recombinant interleukin-2 based immunotherapy regimens after nephrectomy. Cases were staged according to the 2002 UICC TNM system, 6th edition.

The medical records were reviewed retrospectively and cause specific survival rates were calculated by the Kaplan-Meier method. The survival distribution was evaluated using T, N and M factors, and the log rank test was used to compare survival curves. To predict cause specific survival Cox proportional hazards regression models were developed using TNM factors. A nomogram predicting 1, 3 and 5-year cause specific survival was developed by repeating analysis on 200 bootstrap samples to decrease overfit bias and determine 95% CIs.[11]

To validate the nomogram a concordance index was estimated to calculate an unbiased measure of the ability of the nomogram to discriminate among patients.[11] Furthermore, calibration was examined by plotting the predictions made by the nomogram against actual 1, 3 and 5-year survival rates, which were measured by the Kaplan-Meier method using 200 bootstrap samples.[11] All tests were done with SPSS®, version 14.0 and R, version 2.6.1.

RESULTS

A total of 447 patients were treated with radical nephrectomy and 98 were treated with partial nephrectomy. Mean followup was 65 months (range 2 to 247). Of the patients 121 were treated with immunotherapy after nephrectomy. Disease was advanced in 130 patients, including 29 with nodal and 46 with distant metastasis, and 60 died of RCC. Overall 1, 3 and 5-year survival was 95.2%, 92.0% and 89.9%, respectively. Table 1 lists patient characteristics.

As calculated by the Kaplan-Meier method, cause specific survival was significantly related to the T, N and M classifications (each $p < 0.001$, fig. 1). T factor was significantly divided (T1a and T1b $p = 0.007$, T1b and T3a $p = 0.008$, T2 and T3b/c $p = 0.015$, and T3b/c and T4 $p = 0.002$) except for T2 and T3a ($p = 0.784$). T, N and M factors were also significant prognostic factors on multivariate analysis using a Cox proportional hazards regression model (table 2). According to the model there was a reversal in the risk of survival between T2 and T3a, namely the T2 HR was greater than the T3a HR (7.00 vs 6.48).

Using the combined TNM factors we developed a nomogram predicting 1, 3 and 5-year cause specific

Table 1. *Patient characteristics*

No. pts	545	
No. sex: (%)		
M	419	(76.9)
F	126	(23.1)
Mean age at diagnosis	58.1	
Mean tumor size (cm)	4.82	
No. nephrectomy type (%):		
Radical	447	(82.0)
Nephron sparing	98	(18.0)
No. adjuvant immunotherapy (%)	121	(22.2)
No. TNM T (%):		
T1a	272	(49.9)
T1b	109	(20.0)
T2	69	(12.7)
T3a	56	(10.3)
T3b	30	(5.5)
T3c	2	(0.4)
T4	7	(1.3)
No. TNM N (%):		
N0	516	(94.5)
N1	14	(2.6)
N2	15	(2.8)
No. TNM M (%):		
M0	499	(91.6)
M1	46	(8.4)

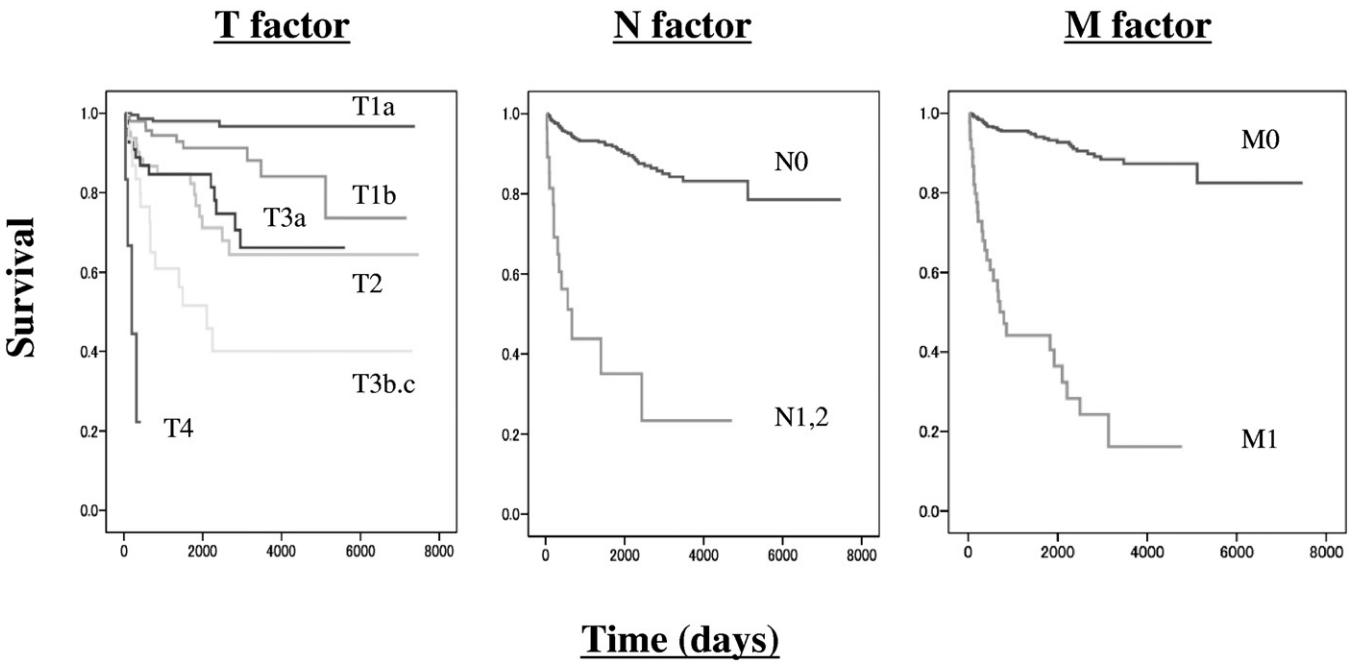

Figure 1. As calculated by Kaplan-Meier method, cause specific survival according to TNM classification was related significantly to T ($p < 0.001$), N ($p < 0.001$) and M ($p < 0.001$) classifications. T factor was significantly divided (T1a and T1b $p = 0.007$, T1b and T3a $p = 0.008$, T2 and T3b/c $p = 0.015$, and T3b/c and T4 $p = 0.002$) except T2 and T3a ($p = 0.784$). One, 3 and 5-year overall survival was 95.2%, 92.0% and 89.9%, respectively.

survival rates by repeating analysis on 200 bootstrap samples (table 3). For example, according to the nomogram the 1, 3 and 5-year cause specific survival rate in cases classified as T1aN0M0 was 99.3%, 98.6% and 97.9%, and in cases classified as T3aN1M1 it was 55.0%, 23.2% and 16.5%, respectively.

Using 200 bootstrap samples we found that the nomogram had excellent ability to discriminate, as evidenced by a concordance index of 0.81. Figure 2 shows the mean nomogram predictions against actual 1, 3 and 5-year patient survival. The 45 degree line represents the ideal predictions. Figure 2 shows that the nomogram was generally well calibrated. However, predictive accuracy may be low in patients predicted to have low survival by the nomogram because the 95% CI of probability of the low survival rate was large.

Table 2. *Cox proportional hazards regression model using TNM factors*

TNM	HR (95% CI)
T ($p < 0.001$):	
T1a	1.00 (Referent)
T1b	2.91 (0.98–8.67)
T2	7.00 (2.50–19.6)
T3a	6.48 (2.22–18.9)
T3b, c	10.39 (3.54–30.5)
T4	38.76 (8.63–174.1)
N ($p = 0.014$):	
N0	1.00 (Referent)
N1,2	2.45 (1.20–4.98)
M ($p < 0.001$):	
M0	1.00 (Referent)
M1	1.81 (3.51–10.6)

DISCUSSION

We developed a preoperative prognostic nomogram based on the TNM classification that predicts cause specific survival in patients with RCC. Recently several RCC nomograms have been developed[1–7] but to our knowledge a preoperative prognostic nomogram that predicts survival in patients with RCC has not been available. Of the published nomograms Karakiewicz et al developed a postoperative nomogram to predict survival in patients with RCC using 6 variables.[5] Because they used a postoperative prognostic variable such as Fuhrman's grade in their nomogram, that nomogram may be useful for postoperative counseling but it would be inconvenient for preoperative counseling. However, by using 6 variables, including postoperative factors, the predictive accuracy of their nomogram may be better than that of our nomogram.

We were able to develop this survival nomogram because our data included 130 advanced cases (29 of nodal and 46 of distant metastasis) and we censored 60 cancer related deaths. Additionally, our nomogram predicts 1, 3 and 5-year cause specific survival, although most published nomograms using the Cox

Table 3. *Preoperative nomogram predicted cause specific survival*

	% Survival (95% CI)		
	1 Yr	3 Yrs	5 Yrs
Stage T1a:			
N0 M0	99.3 (98.8–99.9)	98.6 (97.8–99.7)	97.9 (96.8–99.6)
N1,2 M0	98.5 (95.0–99.7)	96.7 (90.7–99.4)	95.6 (86.9–99.0)
N0 M1	95.3 (91.4–99.0)	91.0 (81.0–97.6)	87.1 (71.3–96.0)
N1,2 M1	91.3 (66.6–97.8)	79.6 (47.5–95.6)	75.1 (32.7–92.9)
Stage T1b:			
N0 M0	98.4 (97.0–99.2)	96.5 (93.9–98.1)	94.9 (90.9–97.5)
N1,2 M0	95.5 (89.9–98.6)	90.7 (80.8–97.4)	87.6 (74.3–96.5)
N0 M1	89.5 (80.3–95.1)	78.4 (58.9–88.0)	69.8 (48.3–85.7)
N1,2 M1	76.0 (41.2–90.2)	53.4 (17.6–81.4)	39.7 (7.4–75.9)
Stage T2:			
N0 M0	95.7 (93.7–98.1)	91.4 (87.1–94.9)	88.4 (83.0–92.9)
N1,2 M0	88.6 (77.5–97.4)	78.8 (58.0–93.0)	70.1 (47.2–91.9)
N0 M1	72.3 (61.6–91.1)	52.9 (32.3–77.7)	40.4 (21.6–61.6)
N1,2 M1	47.8 (11.2–82.2)	21.5 (1.3–58.1)	13.9 (0.1–52.2)
Stage T3a:			
N0 M0	95.7 (93.0–98.3)	90.6 (85.5–96.0)	87.7 (81.4–94.0)
N1,2 M0	89.5 (79.3–97.0)	78.4 (57.5–95.1)	70.4 (40.3–92.2)
N0 M1	73.4 (55.3–91.8)	52.2 (26.4–80.6)	39.9 (16.3–72.7)
N1,2 M1	55.0 (9.4–82.4)	23.2 (0.5–72.8)	16.5 (0.1–59.9)
Stage T3b, c:			
N0 M0	93.3 (88.7–98.3)	86.0 (79.5–95.5)	81.4 (72.7–93.9)
N1,2 M0	85.8 (60.0–95.0)	72.7 (39.1–87.1)	63.5 (26.2–83.0)
N0 M1	62.3 (40.0–88.4)	39.1 (15.6–72.3)	26.1 (6.4–58.7)
N1,2 M1	35.8 (1.8–64.2)	11.0 (0.1–42.4)	5.2 (0.0–36.8)
Stage T4:			
N0 M0	70.3 (22.5–94.4)	50.3 (7.4–88.8)	34.4 (2.6–84.4)
N1,2 M0	48.2 (0.7–74.9)	18.6 (0.0–60.2)	11.1 (0.0–50.3)
N0 M1	14.4 (0.0–67.2)	1.7 (0.0–40.2)	0.3 (0.0–27.3)
N1,2 M1	1.1 (0.0–13.5)	0.0 (0.0–2.0)	0.0 (0.0–0.5)

proportional hazards regression model predict only 5-year outcomes. This increase in prognostic information may be useful for physicians and patients when discussing treatment or obtaining informed consent.

In the last decade factors associated with RCC prognosis have been discussed. Stage, histological grade and type, and performance status are now well-known and commonly used.[12] Today stage is essentially determined by the UICC TNM system. Several groups have evaluated the 1997 TNM staging system and concluded that the classification is a significant predictor of cause specific survival in RCC cases.[9,13,14] In 2002 a modification of this system in the primary tumor classification with T1 cancer subclassified into T1a and T1b was confirmed to have better prognostic ability than the previous 1997 staging system.[15] In our cases the T, N and M of the 2002 system were similarly significant prognostic variables for RCC on univariate and multivariate analysis. As for T1a and T1b, T1a provided a significantly better prognosis than T1b ($p = 0.007$, fig. 1). Also, the T1a HR was almost 3 times higher than the T1b HR (1.00 vs 2.91, table 2).

In this study 121 patients were treated with interferon-α or recombinant interleukin-2 based immunotherapy regimens after nephrectomy. Recently the identification of molecular mechanisms underlying the carcinogenesis of RCC has provided a rationale for new, molecule targeted therapies. The Food and Drug Administration has approved the multikinase inhibitors sorafenib and sunitinib, and the mammalian target of rapamycin inhibitor temsirolimus for metastatic RCC. Therefore, in patients with advanced disease using probabilities based on our nomogram may improve the efficacy of these multikinase inhibitors or mammalian target of rapamycin inhibitor in the future.

To develop the nomogram we performed multivariate analysis using Cox proportional hazards regression models. The HR of T2 was greater than that of T3a (7.00 vs 6.48). Although there are a few reports of multivariate analysis in patients with RCC, the previous nomogram also shows that pT2 has higher values than pT3a, which is in concert with our result.[1] Some groups reported that survival in patients with T3a fat disease is significantly better than in those with T3a adrenal disease.[16,17] It was also shown that the survival of patients with adrenal gland involvement was similar to that of those with tumors involving adjacent organs, currently staged as pT4. These reports suggested that RCC tumors with direct adrenal invasion should be classified as pT4.[16] Additional revision of T3a in the 2002 TNM system, for example, incorporating T3a fat disease into T1 or T2 and T3a adrenal disease into T4, may be required to optimize staging and improve prognostic information.

Several nomograms have been published with the forms classified in probability tables such as the Partin tables[18] and probability nomograms such as the Kattan nomogram.[1,19] Probability tables such as the Partin tables have an advantage in that probabilities are directly expressed but continuous variables cannot be used as is. Continuous variables should be categorized into some groups for use in probability tables. A probability nomogram such as the Kattan nomogram can produce a continuous probability and use continuous variables as they are but probabilities are not directly expressed. Therefore, calculations are required to determine the probability. Our nomogram is presented as probability tables because T, N and M factors were nominal variables and it can directly express cause specific survival.

Using 200 bootstrap samples we found that our nomogram has excellent ability to discriminate, as evidenced by a concordance index of 0.81. It is generally well calibrated, although validation was internal and used the same data set that was used to

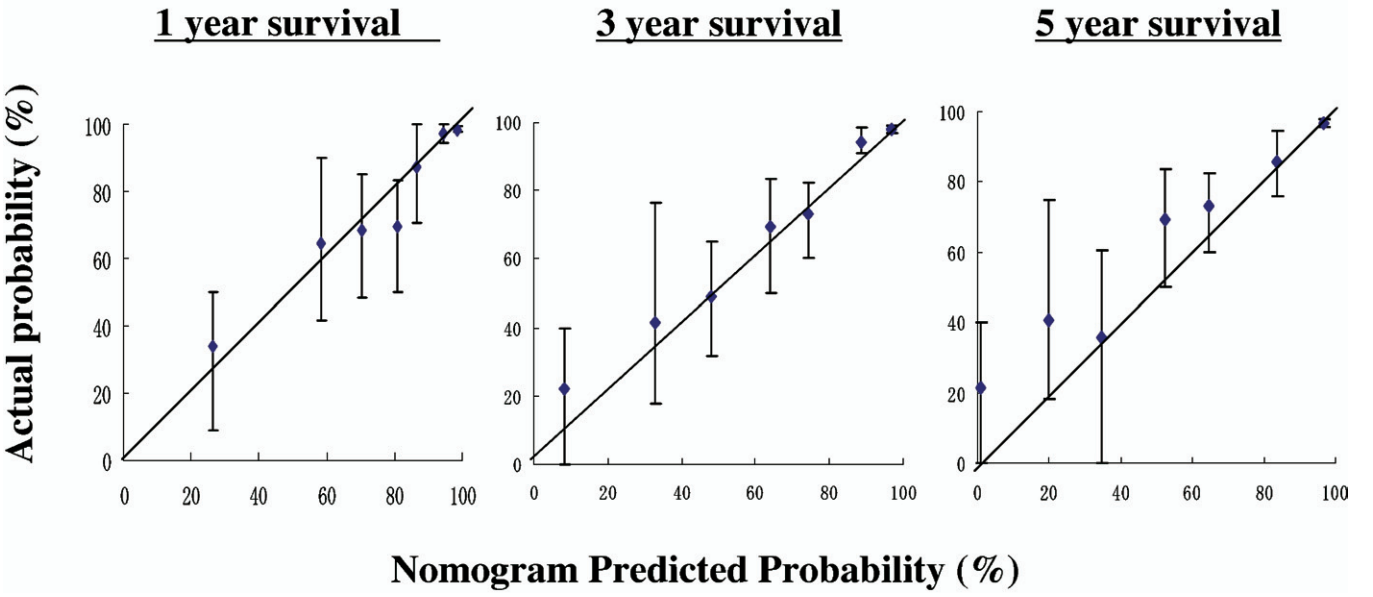

Figure 2. Nomogram calibration. X axis indicates nomogram predicted cause specific survival probability. Y axis indicates corresponding cause specific survival probability. Line at 45 degrees represents ideal prediction. Vertical lines represent 95% CI.

develop the nomogram. Several nomograms have already been validated using different data sets from other institutions or of other populations. A group from Memorial Sloan-Kettering Cancer Center validated their nomogram using a data set from Columbia University and reported that the concordance index was 0.82.[3] They concluded that their nomogram was generally well calibrated. On the other hand, Hupertan et al validated the Kattan RCC nomogram in a population of French patients and reported that the concordance index was 0.607.[20] They concluded that there was a discrepancy between predicted recurrence-free survival in their population of patients. Therefore, it is necessary to perform external validation to estimate the accuracy of our nomograms using data from different institutions or on other populations.

CONCLUSIONS

We developed a preoperative prognostic nomogram for RCC. The preoperative information in the nomogram may be important for obtaining informed consent from patients with RCC who have indications for surgery. However, it is necessary to perform external validation to estimate the accuracy of our nomogram at different institutions and in other populations.

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EDITORIAL COMMENT

This study complements the existing RCC prediction model literature by adding a preoperative tool that predicts disease specific survival. The tool seems to predict reasonably well and clearly better than counseling all patients as if they have the same preoperative prognosis. Of some concern are predictions in patients with T3b/c or T4 disease since there were only 32 and 7 of them, respectively. Also, the N1/2 group is relatively small with 29 patients. Future tools should consider incorporating imaging results and their potential impact on predictive accuracy.

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