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Pre-operative nomogram predicting 12-year probability of metastatic renal cancer

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Abstract

Purpose—For patients with renal masses localized to the kidney, there is currently no pre-operative tool to predict the likelihood of metastatic recurrence following surgical intervention. The primary goal of this study was to develop a predictive model that could be used in the pre-operative setting.

Methods—We pooled institutional databases from Memorial Sloan-Kettering and Mayo Clinic and identified 2,517 patients with renal masses and no concurrent evidence of metastases, who underwent radical or partial nephrectomy and with complete data. Cox proportional hazard regression analyses were used to model pre-operative clinical and radiographic characteristics as predictors for development of metastases following nephrectomy. Internal validation was performed with a statistical bootstrapping technique.

Results—Metastatic recurrence developed in 340 of the 2517 patients. Median follow-up for patients without metastatic recurrence was 4.7 years. A nomogram was developed using pre-operative characteristics to predict the 12-year likelihood of post-operative metastatic recurrence, with a concordance index (CI) of 0.80. In contrast, the concordance index of pre-operative TNM staging was 0.71. Size of the primary renal mass, evidence of lymphadenopathy or necrosis on pre-operative imaging and the mode of presentation were important predictors for the subsequent development of metastases.

Conclusions—We present a pre-operative nomogram that accurately predicts the development of metastatic recurrence following nephrectomy. This nomogram may be potentially useful to identify high-risk patients for clinical trials in neoadjuvant setting.

Keywords

nomogram; renal masses; nephrectomy; metastasis

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Introduction

With the widespread advent of non-invasive abdominal imaging modalities such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), the incidence of renal cell carcinoma (RCC) has been increasing worldwide.^{1–3} In 2007, in the United States alone, 51,190 new cases of renal cancers will be detected.¹ A majority of these renal masses (50–80%) will have been detected incidentally as small tumors in asymptomatic patients, resulting in a stage and a size migration.^{4–5}

The current standard for management of a patient with a renal mass and no evidence of metastatic disease remains surgical extirpation with a partial or radical nephrectomy.^{2–3} Among the patients undergoing nephrectomy for clinical localized renal cell carcinoma, 20 to 40% will develop clinically detectable metastases.^{2,6} Historically, patients with metastatic RCC face a poor prognosis, with a median survival of 6 to 10 months and a 2-year survival of 10 to 20%.⁷

Predictive models for recurrence or development of metastatic disease of renal cell carcinoma following definitive surgical intervention with a partial or radical nephrectomy are useful for patient counseling, clinical assessment of the need for additional therapies and clinical trial design. Post-operative predictive models including the MSKCC post-operative prognostic nomogram, the Mayo clinic SSIGN score and UCLA UISS score were created using clinical stage, tumor histology, pathologic tumor size, pathologic stage and grade, pathologic necrosis, ECOG performance score and symptomatic presentation to predict the freedom from disease recurrence or overall survival after definitive therapy.^{8–13}

Since the various post-operative predictive tools are based on pathologic variables, their utility in the pre-operative setting is limited. A pre-operative tool that predicts the likelihood of metastatic disease following definitive surgical therapy would be useful to risk-stratify patients prior to surgery. In this report, using pre-operative clinical and radiologic parameters, we have developed a nomogram that predicts the likelihood of a metastatic recurrence following a partial or radical nephrectomy.

Materials and Methods

Institutional review board approval was obtained from both participating sites providing the necessary institutional data use agreements before initiation of the study. To collect data for nomogram development, we designed a minimal pre-operative data set, specified in a relational database. Only de-identified datasets were transferred between institutions. At data transfer, the initial evaluation of the data sets allowed for the detection of missing variables, which were then resolved and a final data set was produced for creation of the nomogram. All pre-operative variables that have been suggested in other studies to influence prognosis of patients with renal masses were included in the predictive model.

All patients undergoing a radical or partial nephrectomy for a renal mass between 1970–2004 at the Mayo Clinic and between 1989–2004 at MSKCC were included in the database. Patients prior to 1994 were excluded from the MSKCC database as the pre-operative size of the renal mass was uniformly not recorded. Pre-operative variables included in the initial

database included patient age and gender, Charlson-Romano comorbidity index, mode of presentation, ECOG performance status and radiologic parameters obtained by pre-operative radiologic evaluation including tumor type (solid v cystic), tumor location, evidence of necrosis on CT scan, evidence of renal vein or IVC involvement, evidence of regional lymphadenopathy, evidence of multifocality, evidence of synchronous bilaterality. While the initial multivariate model included all variables, exclusion of variables like year of surgery, age, charlson-Romano index, ECOG performance status, multifocality, tumor location, tumor type, venous involvement did not alter the discriminant performance of the model and were excluded from their final model in order to generate a more compact nomogram.

Outcomes were measured in terms of metastasis: patients were either alive without metastases, had documented metastatic recurrence, or dead without metastasis. Only patients with incomplete datasets were censored.

Statistical Methods

The Kaplan-Meier method was used to calculate the probability of freedom from metastasis. Cox proportional hazards regression was used for multivariable analysis. Ordinal and continuous variables were fit using restricted cubic splines to relax the linearity assumptions. No variable selection was initially performed. This Cox model was the basis for the nomogram. In other words, the nomogram is a graphical representation of the Cox model. Coefficients from the Cox model were rescaled to a 100 point scale to make them more user friendly.

Nomogram validation comprised two tasks to evaluate discrimination and calibration. First, discrimination was quantified with the concordance index (CI). On a 0.5 to 1.0 scale identical to that of the area under a receiver operating characteristic curve, the CI provides the probability that, in a randomly selected pair of patients in which one patient develops metastasis before the other, the patient who developed metastasis first had the worse predicted outcome from the nomogram. We used bootstrapping to obtain a relatively unbiased estimate of the concordance index and the calibration plot, as without bootstrapping, we might be looking at overfit rather than expected accuracy in future patients.

Second, calibration was assessed. This was done by grouping patients with respect to their nomogram-predicted probabilities and then comparing the mean of the group with the observed Kaplan-Meier estimate of freedom from metastasis. All patients were used for calibration. Again, bootstrapping correction was used for this task to correct for the overfit. All analyses were performed using S-Plus 2000 Professional software (Statistical Sciences, Seattle, WA) with the Design and Hmisc libraries added.

Results

Overall, 5048 patients undergoing definitive surgical intervention for renal masses from the MSKCC and Mayo clinic institutional databases were pooled. 523 patients were excluded because of documented evidence of metastatic disease at the time of surgery. An additional 366 patients from the MSKCC database were excluded because of the consistent lack of data

on pre-operative clinical size of renal masses prior to 1994. Of the remaining 4159 patients, pre-operative data was missing on 1642 patients, as shown in Table 1. Overall, 2517 had complete data on all pre-operative characteristics including age, gender, clinical size of the renal mass, mode of presentation, evidence of necrosis within the tumor and evidence of lymphadenopathy and formed our cohort for analyses.

The demographics of the 2517 patients with clinically localized renal masses, who were treated with operative intervention, are shown (Table 1). The 2517 patients included 1581 patients who underwent a radical nephrectomy and 936 who underwent a partial nephrectomy. Only 184 of these radical and partial nephrectomies were performed laparoscopically; the rest were performed using open techniques.

Of the 2517 patients managed surgically, 1698 patients are still alive and 479 patients died with no evidence of metastatic recurrence. The remaining 340 patients had metastatic recurrence following definitive surgical intervention. The 12-year freedom from metastasis was 70% (95% CI 68 to 72%) for the combined cohorts (Figure 1), 70% (95% CI 68 to 72%) for the Mayo cohort and 65% (95% CI 58 to 72%) for the MSKCC cohort. The median follow-up for patients without any evidence of metastatic recurrence was 4.7 years in the combined cohorts, 7.4 years in the Mayo cohort and 2.3 years in the MSKCC cohort.

Pre-operative characteristics including size of the renal mass (HR 1.20 (95% CI 1.16–1.23), $p < 0.001$), mode of presentation (HR 1.89 (95% CI 1.64–2.18), $p < 0.001$), evidence of necrosis within the tumor (HR 1.73 (95% CI 1.58–1.88), $p = 0.009$) and evidence of lymphadenopathy (HR 2.93 (95% CI 2.16–3.98), $p < 0.001$) were significantly associated with metastatic recurrence after nephrectomy. A nomogram incorporating these variables that may influence prognosis of patients with renal masses is shown in Figure 2.

The bootstrap corrected concordance index of the model developed across 2517 patients was 0.8. A cross validation sensitivity analysis between centers revealed that the CI varied from 0.89 when the MSKCC series was used as test set for the model based on the Mayo to 0.76 when the Mayo series was used as test set for the model based on the MSKCC. Further, we also examined patients from a similar time frame, 1994 to 2004, in both centers and found that the CI of the nomogram was similar in both datasets. As illustrated in Figure 3, the nomogram seems to have very good calibration.

In comparison, the concordance index for the clinical TNM staging was 0.71. The distribution of nomogram predicted probabilities is shown for each clinical stage in Figure 4. The variation in risk appears to be more pronounced for patients in clinical stages II and III.

Discussion

The natural history of small renal masses is not known. Several authors have reported that small localized primary renal masses have a slow rate of growth.^{4,5,14} In one meta-analysis of 234 renal masses, the average growth rate was 0.28 cm/year.⁵ Based on these small retrospective studies, increasingly, patients with small renal masses are being offered observation rather than intervention. Additionally, ablative approaches such radio frequency, cryo- or high intensity focused ultrasound are gaining popularity as management options for

patients with these small renal masses, although the true efficacy of these approaches is not known due to limited follow-up and consistent lack of pathological confirmation of treatment effect.¹⁵ The oncologic efficacy of these approaches in preventing metastasis and subsequently cancer-specific death must ultimately be compared to the “standard” of a radical or partial nephrectomy.

The nomogram developed here demonstrates the utility of definitive surgical intervention in the management of patients with localized renal masses and may be useful for counseling patients. For example, a patient with an incidental 3-cm renal mass, and no concurrent adverse clinical or radiographic features, has a 98% predicted probability of being free from metastatic recurrence at 12 years. In the current era of incidental renal masses, such a patient would be typical of those being offered observation. Our predictive model indicates that surgical intervention for this patient is associated with excellent long-term prognosis. Alternative management options must yield similar long-term oncologic outcomes or be considered inferior.

The pooling of data from two centers of excellence has revealed some interesting findings. Despite differences between patients at the two centers in the mode of presentation, pre-operative size of the renal mass, detection of lymphadenopathy and necrosis on imaging studies, the 12 year-metastasis-free survival is similar for both centers. Our finding that the CI of the nomogram was similar in both datasets from 1994–2004 may reflect the ongoing tumor stage and size migration from the early 1970s.

Nomograms are statistical models specifically designed to maximize predictive accuracy. In contrast to predictive models that assign prognosis based on risk groups, nomograms provide prognostic information based on a combination of variables that allow for a more individualized prediction of outcome. Multiple studies have demonstrated the superiority of more complex predictive modeling in providing improved accuracy compared with risk group assignment techniques.¹⁶ The nomogram is precise and punctual instrument to estimate the prognosis of a single patient. In this study, patients in clinical stages II and III have a wide variation in their nomogram-predicted risk of developing metastasis: TNM staging alone is inadequate in delineating which of these patients need more aggressive management.

The utility of the pre-operative nomogram may be best illustrated with another example. A female with an incidentally discovered 3-cm renal mass and no adverse features on imaging has 45 points or 96% chance of being metastasis-free at 12 years after definitive surgical intervention. A male with 4-cm renal mass diagnosed upon evaluation for flank pain or hematuria and with evidence of lymphadenopathy and necrosis within the mass on imaging has 105 points or a 60% chance of being metastasis-free at 12 years after definitive surgical intervention. Both patients have similar clinical stages, yet very different likelihood of developing metastatic disease. Pre-operative counseling of their individualized risks helps the patient and physician prepare for the need for additional therapies following surgical intervention.

Since the characterization of molecular pathways involved in renal tumors,^{17–18} novel therapies targeted against specific targets within the pathway have been developed that have shown efficacy in treating metastatic renal tumors.^{18–19} The utility of these agents including Sunitinib and Sorafenib in a neoadjuvant setting has yet to be explored. Patients at higher risk of developing metastatic disease may be counseled about the potential for metastases and the potential need for adjuvant therapy after surgery. The nomogram described here may be potentially used for selecting patients for future neoadjuvant clinical trials. For patients with a renal mass with clinical TNM stage II or stage III, the nomogram offers better discrimination of the likelihood of cure with surgery alone and identifies patients who may benefit from additional therapies.

These data have several limitations that must be examined prior to widespread contemporary application of this predictive model. The population described in this report represents patients undergoing surgery at tertiary academic medical centers, and inherent selection bias must be considered. The thirty-five year time horizon of this pooled database incorporates many more advanced patients than typically seen now. With the ongoing stage migration since the early 1970s, renal masses are increasingly being detected at earlier stages and at smaller sizes. In theory, our nomogram corrects for this stage migration and is able to identify 74% of Stage III, 51% of Stage II and 2% of Stage I patients who have greater than a 40% chance of developing metastases within 12 years following surgery. Thus, the nomogram can discriminate the “high-risk cohort” who may benefit from additional therapeutic intervention.

With advances in imaging, metastatic disease may be detected at earlier time points, thus skewing the contemporary outcomes. Additionally, advances in surgical technique may influence outcomes of these patients. Thus, the predictions of the nomogram developed here may be underestimate outcomes for patients treated contemporaneously. However, adding year of surgery to the prediction model had a trivial effect: consequently this variable was excluded for ease of use. External validation of this dataset using another contemporary cohort may be useful.

In developing this nomogram, we have used readily available clinical and radiologic parameters for outcome prediction. Due to the retrospective nature of the study, the removal of 1642 patients with incomplete data may represent source of bias. The metastatic rate in the excluded 1642 patients with incomplete data was 16% (243/1642), which is higher than that in the 2517 patients used for the data set (13.5% or 340/2517). Additional radiographic features that may improve the accuracy of future nomograms may include evidence of vascular flow within the renal mass on Doppler ultrasonography, G250- labeled scans, evidence of renal vein involvement and adrenal involvement.²⁰

We have deliberately not incorporated any pathologic information from the nephrectomy specimen in our predictive model, as this information is not available pre-operatively. We recognize that inclusion of biopsy information in future nomograms may further increase the prognostic accuracy.

Despite these limitations, the nomogram developed here predicts the outcomes of patients treated with nephrectomy. The predicted outcomes may be used as a standard against which all other options for the management of clinically localized renal masses must be measured against. With a dataset of over forty-five hundred patients and concordance index of 0.80, the nomogram appears to be robust and accurate. Additionally, it is superior to the conventional TNM staging and offers a more accurate predictive tool than available techniques.

Conclusion

We have developed a new prognostic pre-operative nomogram that predicts the likelihood of metastatic recurrence within 12 years of definitive surgical intervention. This nomogram may help counsel patients pre-operatively about their subsequent risk of developing metastatic disease and help define the post-operative follow-up guidelines. Additionally, the nomogram may be useful for designing future clinical trials examining neoadjuvant therapies. Finally, the nomogram establishes a predictive model for outcomes of patients undergoing surgery, which can be used to evaluate the utility of alternative non-surgical approaches, including observation, for patients with clinically localized renal masses.

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Figure 1. Kaplan Meier analyses evaluating the proportion of patients who are free of metastatic recurrence over time with numbers at risk for each time point.

Figure 2.
Pre-operative nomogram predicting Freedom for metastatic recurrence at 12 years following definitive surgical management.

Figure 3. Model Calibration

Calibration curves for the nomogram. X-axis is nomogram predicted probability. Patients were grouped by quartiles of predicted risk. Y-axis is actual metastasis-free probability as estimated by the Kaplan-Meier method. Solid line: actual nomogram; dotted line: ideal nomogram. Vertical bars represent 95% confidence intervals (95% CI). For each quartile of both nomogram predictions, the 95% CIs overlap the diagonal ideal line, where predicted metastasis-free probability would exactly match actual metastasis-free probability.

Figure 4. Histogram showing distribution of nomogram predicted probabilities of 12-year freedom from metastatic disease within the American Joint Committee on Cancer (AJCC) clinical stages based on TNM classification.

Table 1

Demographics of the cohort

Parameter	Mayo Clinic	MSKCC	Total	Missing data #
Years covered	1970–2004	1994–2004		
Number of patients	1558	959	2517	
Age, Median (range)	64 (21–91)	63 (19–89)	64 (19–91)	0
% male gender	68%	63%	66%	0
Presenting symptoms:				8
% Incidental	36%	72%	51%	
% Localized	39%	24%	33%	
% Systemic	25%	4%	16%	
Size of renal mass on imaging in cm Median (range)	5.5 (0.5–20)	4.9 (0.8–18)	5.3 (0.5–20)	727
% with Lymphadenopathy on imaging	3%	11%	6%	1378
% with evidence of necrosis on imaging	5%	13%	8%	725