Preoperative Nomogram Predicting 12-Year Probability of Metastatic Renal Cancer

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Purpose: For patients with renal masses localized to the kidney there is currently no preoperative tool to predict the likelihood of metastatic recurrence following surgical intervention. We developed a predictive model that could be used in the preoperative setting.

Materials and Methods: We pooled institutional databases from Memorial Sloan-Kettering and Mayo Clinic, and identified complete data on 2,517 patients with renal masses and no concurrent evidence of metastases who underwent radical or partial nephrectomy. Cox proportional hazard regression analyses were used to model preoperative 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 2,517 patients. Median followup for patients without metastatic recurrence was 4.7 years. A nomogram was developed using preoperative characteristics to predict the 12-year likelihood of postoperative metastatic recurrence with a concordance index of 0.80. In contrast, the concordance index of preoperative TNM staging was 0.71. Size of the primary renal mass, evidence of lymphadenopathy or necrosis on preoperative imaging and the mode of presentation were important predictors for the subsequent development of metastases.

Conclusions: We present a preoperative nomogram that accurately predicts the development of metastatic recurrence following nephrectomy. This nomogram may be potentially useful to identify and counsel patients at high risk for recurrence.

Key Words: nomograms; carcinoma, renal cell; nephrectomy; neoplasm metastasis

With the widespread advent of noninvasive abdominal imaging modalities such as ultrasonography, computed tomography and magnetic resonance imaging, the incidence of renal cell carcinoma has been increasing worldwide. In 2007 in the United States alone 51,190 new cases of renal cancers were detected. A majority of these renal masses (50% to 80%) will have been detected incidentally as small tumors in asymptomatic patients, resulting in a stage and a size migration.

The current standard for treatment of a patient with a renal mass and no evidence of metastatic disease remains surgical extirpation with partial or radical nephrectomy. Of the patients undergoing nephrectomy for clinical localized renal cell carcinoma, clinically detectable metastases will develop in 20% to 40%. 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%.

Predictive models for recurrence or development of metastatic disease of renal cell carcinoma following definitive surgical intervention with partial or radical nephrectomy are useful for patient counseling, clinical assessment of the need for additional therapies and clinical trial design. Postoperative predictive models including the MSKCC postoperative prognostic nomogram, the Mayo Clinic SSIGN (stage, size, grade and necrosis) score and UCLA UISS (University of California-Los Angeles Integrated Staging System) score were created using clinical stage, tumor histology, pathological tumor size, pathological stage and grade, pathological necrosis, ECOG performance score and symptomatic presentation to predict the freedom from disease recurrence or overall survival after definitive therapy.

Since the various postoperative predictive tools are based on pathological variables, their usefulness in the preoperative setting is limited. A preoperative tool that predicts the likelihood of metastatic disease following definitive surgical therapy would be useful to risk stratify patients before surgery. In this report using preoperative clinical and radiological parameters we developed a nomogram that predicts the likelihood of metastatic recurrence following 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 preoperative data set specified in a relational database. Only

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de-identified data sets 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 preoperative 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 radical or partial nephrectomy for a renal mass between 1970 and 2004 at the Mayo Clinic and between 1989 and 2004 at MSKCC were included in the database. Patients before 1994 were excluded from the MSKCC database as the preoperative size of the renal mass was not recorded uniformly. Preoperative variables included in the initial database included patient age and gender, Charlson-Romano comorbidity index, mode of presentation, ECOG performance status, and radiological parameters obtained by preoperative radiological evaluation including tumor type (solid vs cystic), tumor location, evidence of necrosis on computerized tomography, evidence of renal vein or inferior vena cava involvement, evidence of regional lymphadenopathy, evidence of multifocality and evidence of synchronous bilaterality. Some of these predictors had numerous missing values which we interpreted as suggestive that they might not be routinely available. Furthermore, they had essentially no impact on the discrimination ability of the nomogram. Specifically variables like year of surgery, age, Charlson-Romano index, ECOG performance status, multifocality, tumor location, tumor type and venous involvement did not alter the discriminant performance of the model, and were excluded from the final model to generate a more compact nomogram.

Outcomes were measured in terms of metastasis. Patients were either alive without metastases, had documented metastatic recurrence or died without metastasis. Patients were censored at time of death without metastasis or last followup without metastasis.

In terms of 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 stepwise variable selection was 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. These coefficients were nearly identical to those obtained from competing risks regression.

Nomogram validation comprised 2 tasks to evaluate discrimination and calibration. Discrimination was quantified with the concordance index. 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 metastasis develops in 1 patient before the other, the patient in whom metastasis developed 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 because without bootstrapping we might be looking at overfit rather than expected accuracy in future patients.

Calibration was then assessed by grouping patients with respect to nomogram predicted probabilities and 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 with the Design and Hmisc libraries added.

### RESULTS

Overall 5,048 patients undergoing definitive surgical intervention for renal masses from the MSKCC and Mayo Clinic institutional databases were pooled. A total of 523 patients were excluded from analysis because of documented evidence of metastatic disease at surgery. An additional 366 patients from the MSKCC database were excluded because of the consistent lack of data on preoperative clinical size of renal masses before 1994. Of the remaining 4,159 patients preoperative data were missing on 1,642 as shown in the table. Overall 2,517 patients had complete data on all preoperative 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 2,517 patients with clinically localized renal masses treated with operative intervention are shown in the table. The 2,517 patients included 1,581 who underwent radical nephrectomy and 936 who underwent partial nephrectomy. Only 184 of these radical and partial nephrectomies were performed laparoscopically, and the rest were performed using open techniques.

Of the 2,517 patients treated surgically 1,698 are still alive and 479 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, 70% (95% CI 68% to 72%) for the Mayo cohort and 65% (95% CI 58% to 72%) for the MSKCC cohort.

<table>
<thead>
<tr>
<th>Cohort demographics</th>
<th>Mayo Clinic</th>
<th>MSKCC</th>
<th>Totals</th>
<th>No. Missing Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
<td>1,585</td>
<td>959</td>
<td>2,517</td>
<td>0</td>
</tr>
<tr>
<td>Median pt age (range)</td>
<td>64 (21–91)</td>
<td>63 (19–89)</td>
<td>64 (19–91)</td>
<td>0</td>
</tr>
<tr>
<td>% Male</td>
<td>68%</td>
<td>63%</td>
<td>66%</td>
<td>0</td>
</tr>
<tr>
<td>Presenting symptoms (%)</td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Incidental</td>
<td>36%</td>
<td>72%</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>39%</td>
<td>24%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>25%</td>
<td>4%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Median renal mass cm on imaging (range)</td>
<td>5.5 (0.5–20)</td>
<td>4.9 (0.8–18)</td>
<td>5.3 (0.5–20)</td>
<td>727</td>
</tr>
<tr>
<td>Lymphadenopathy on imaging (%)</td>
<td>3</td>
<td>11%</td>
<td>6%</td>
<td>1,378</td>
</tr>
<tr>
<td>Evidence of necrosis on imaging (%)</td>
<td>5</td>
<td>13%</td>
<td>8%</td>
<td>725</td>
</tr>
</tbody>
</table>
cohort (fig. 1). The median followup 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.

Preoperative 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 2,517 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. Furthermore, we also examined patients from a similar time, 1994 to 2004, in both centers and found that the CI of the nomogram was similar in both data sets. As illustrated in figure 3 the nomogram seems to have good calibration.

In comparison, the concordance index for clinical TNM staging was 0.71. The distribution of nomogram predicted probabilities is shown for each clinical stage in figure 4. The

![Fig. 1. Kaplan-Meier analyses evaluating proportion of patients who are free of metastatic recurrence over time with numbers at risk for each point.](image1)

![Fig. 2. Preoperative nomogram predicting freedom from metastatic recurrence at 12 years following definitive surgical management.](image2)
variation in risk appears to be more pronounced for 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. In a meta-analysis of 234 renal masses the average growth rate was 0.28 cm per year. Based on these small retrospective studies, patients with small renal masses are increasingly being offered observation rather than intervention. Additionally, ablative approaches such as radio frequency, cryoablation or high intensity focused ultrasound are gaining popularity as treatment options for patients with these small renal masses.

Fig. 3. Model calibration. Calibration curves for 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 Kaplan-Meier method. Solid line represents actual nomogram. Broken line represents ideal nomogram. Vertical bars represent 95% CI. For each quartile of both nomogram predictions, 95% CIs overlap diagonal ideal line where predicted metastasis-free probability l would exactly match actual metastasis-free probability.

Fig. 4. Histogram showing distribution of nomogram predicted probabilities of 12-year freedom from metastatic disease within American Joint Committee on Cancer clinical stages based on TNM classification.
masses, although the true efficacy of these approaches is not known due to limited followup and consistent lack of pathological confirmation of treatment effect. The oncological efficacy of these approaches in preventing metastasis and subsequently cancer specific death must ultimately be compared to the standard of radical or partial nephrectomy.

The nomogram developed here demonstrates the usefulness of definitive surgical intervention in the treatment of patients with localized renal masses and may be useful for counseling patients. For example, a patient with an incidentally 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 an excellent long-term prognosis. Alternative management options must yield similar long-term oncological outcomes or be considered inferior.

The pooling of data from 2 centers of excellence reveals some interesting findings. Despite differences between patients at the 2 centers in mode of presentation, preoperative 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 data sets from 1994 to 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. The nomogram is a precise and punctual instrument to estimate the prognosis of a single patient. In this study patients with clinical stage II and III disease have wide variation in nomogram predicted risk of metastasis. TNM staging alone is inadequate in delineating which of these patients need more aggressive management.

The usefulness of the preoperative 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 a 96% chance of being metastasis-free at 12 years after definitive surgical intervention. A male with a 4 cm renal mass diagnosed on 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 different likelihoods of metastatic disease developing. Preoperative 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, novel therapies targeted against specific targets within the pathway have been developed that have shown efficacy in treating metastatic renal tumors. The usefulness of these agents including sunitinib and sorafenib in a neoadjuvant setting has yet to be explored. Patients at higher risk for 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 those who may benefit from additional therapies.

These data have several limitations that must be examined before 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 35-year time horizon of this pooled database incorporates many more advanced cases 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 cases with a greater than 40% chance of metastases within 12 years following surgery. Thus, the nomogram can determine 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 the outcomes of these patients. Thus, the predictions of the nomogram may underestimate outcomes for patients treated contemporaneously. However, adding year of surgery to the prediction model had a trivial effect, and so this variable was excluded for ease of use. External validation of this data set using another contemporary cohort may be useful.

In developing this nomogram we used readily available clinical and radiological parameters for outcome prediction. Due to the retrospective nature of the study the removal of 1,642 patients with incomplete data may represent a source of bias. The metastatic rate in the excluded 1,642 patients with complete data was 16% (243 of 1,642), which is higher than that in the 2,517 patients used for the data set (13.5% or 340 of 2,517). Additional radiographic features to improve the accuracy of future nomograms may include evidence of vascular flow within the renal mass on Doppler ultrasonography or G250 labeled scans. Furthermore, we have liberately not incorporated any pathological information from the nephrectomy specimen in our predictive model as this information is not available preoperatively. We recognize that inclusion of biopsy information in future nomograms may further increase 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 data set of more than 4,500 patients and a 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.
CONCLUSIONS

We have developed a new prognostic preoperative nomogram that predicts the likelihood of metastatic recurrence within 12 years of definitive surgical intervention. This nomogram may help counsel patients preoperatively about the subsequent risk of metastatic disease and help define the postoperative followup 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 usefulness of alternative nonsurgical approaches, including observation, for patients with clinically localized renal masses.

Abbreviations and Acronyms

CI = concordance index 
ECOG = Eastern Cooperative Oncology Group 
MSKCC = Memorial Sloan-Kettering Cancer Center 
RCC = renal cell carcinoma

REFERENCES


EDITORIAL COMMENT

Prediction of the natural history of treated RCC is important. Pretreatment models predicting the prognosis of RCC are crucial for discriminating between those in whom the proposed therapy might fail and those who are likely to enjoy a lengthy remission or a cure. Raj et al provide us with a model that proposes predicting the risk of metastatic progression after nephrectomy. The model relies on pretreatment variables and has not yet been externally validated. This model represents a highly valuable stepping stone toward more discriminant attempts at risk stratification that could assist the clinician in the complex and challenging decision making process in which surveillance, surgery and nonextirpative treatment modalities are considered. Since the model exclusively relies on surgical patients, alternative treatment modalities cannot be validly compared to surgery. However, the model proves the point that the prediction of the natural history of treated RCC can be accomplished with excellent accuracy (80%). The elaboration of similar models in patients treated with nonextirpative treatment modalities as well as those treated with surveillance would enable comparisons of cancer control between these alternatives.

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