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Preoperative Nomogram Predicting 12-year Probability of Metastatic Renal Cancer – Evaluation in a Contemporary Cohort

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Abstract

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Conflict of Interest and Disclosure Statement

Oguz Akin holds stock options and serves as a scientific advisor for Ezra AI, Inc., which is developing Artificial Intelligence algorithms and software unrelated to the research being reported.

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Objectives—Preoperative models, based on patient and tumor characteristics, predict risk for adverse outcomes after nephrectomy. Changes in renal tumor characteristics over the last decades, warrant further evaluation using contemporary cohorts.

We aimed to validate a previously published preoperative nomogram predicting 12-year metastasis-free probability after nephrectomy for localized renal tumors in a contemporary cohort.

Patients and Methods—After obtaining institutional review board approval, data of 1,760 patients who underwent nephrectomy for a localized renal mass between 2005 - 2011 were reviewed. Preoperative images were evaluated for the presence of tumor necrosis, lymphadenopathy and tumor size.

The study outcome was metastatic-free probability. Model discrimination was assessed with Gonen and Heller's concordance probability estimate, and calibration was evaluated.

Results—The cohort included 1,102 male and 658 female patients with a median age of 60 years. Most patients presented incidentally (84%). On imaging, 3% had evidence of lymphadenopathy, 55% had necrosis and median tumor diameter was 3.7cm (IQR:2.5, 5.5).

Median follow-up in non-metastatic patients was 7.7 years (IQR 5.3, 9.7). Estimated 12-year metastatic-free probability was 88% (86% - 90%). The model showed strong discrimination (CPE: 0.77), and fair calibration. The time-dependent ROC curves showed strong discrimination at all time points and the AUC for year 12 was 0.83 (95% CI:0.78-0.89).

Conclusions—We validated the preoperative nomogram of 12-year metastasis-free probability in a contemporary cohort despite different tumor characteristics.

Future studies should evaluate the role of preoperative risk stratification in patient selection for neoadjuvant treatment.

Keywords

Metastases; Nephrectomy; Nomogram; Outcome; Preoperative; Renal cell carcinoma

Introduction

Over 70% of renal tumors are diagnosed at an early stage.[1] Despite curative surgical treatment, approximately one third of patients will develop metastatic disease at a follow-up of 10 years.[2] Neoadjuvant immunotherapy has an evolving role as a mean to improve outcome in solid malignancies and is currently evaluated for renal cell carcinoma (RCC).[3, 4] However, the use of immunotherapy, especially when combining PD-1 and CTLA-4 blockade, is associated with substantial toxicity necessitating careful patient selection prior to treatment.[3] Preoperative risk stratification can identify high-risk patients who are suitable candidates for neoadjuvant trials.[5]

Current preoperative predictive models rely on patient and tumor characteristics on imaging to predict the risk of metastases and cancer related mortality after nephrectomy.[6-13] In a previous publication from the Mayo Clinic and our center, Raj et. al. reported a preoperative nomogram for predicting the 12-year metastatic free probability (MFP) for patients with localized renal tumors. The nomogram included gender, mode of presentation, evidence of

lymphadenopathy, evidence of necrosis and tumor size based on preoperative imaging.[8] Despite demonstrating an improved predictive capability over clinical stage alone, this nomogram has not been validated.

Over the last decades there has been a change in the characteristics of renal tumors at time of diagnosis including a higher rate of incidental findings and a decrease in tumor size and stage.[1, 14, 15] In light of these changes, it is unknown whether preoperative nomograms, published over a decade ago, are still accurate in the contemporary setting.

In the current study we aimed to validate our previously reported nomogram, published by Raj et. al. [8], using a contemporary cohort of patient with localized renal masses.

Patients and Methods

After obtaining institutional review board approval we reviewed our prospectively collected nephrectomy database and identified 2,048 consecutive patients who underwent a partial or radical nephrectomy at Memorial Sloan Kettering Cancer Center for a localized renal mass between the years 2005 and 2011. Patients treated for bilateral renal tumors (n=56), with metastatic disease from a source other than kidney (n=27), previous procedures on their ipsilateral kidney (n=6) and without preoperative imaging (n=199) were excluded, leaving a total of 1,760 patients for analysis (Supplementary Figure 1).

Pre-operative patient data including age, gender, race and mode of presentation were collected. Mode of presentation was classified as incidental (no symptoms), local (hematuria, flank pain, palpable mass), or systemic (weight loss, anorexia, asthenia, fever), based on a validated classification system.[16] Preoperative cross-sectional imaging was reviewed by radiologists (CD, OA) for the presence of lymphadenopathy (yes/no), necrosis (yes/no), and tumor size (cm). Lymphadenopathy was identified when the short axis diameter of the node was greater than 1 cm, the node had irregular shape and/or enhancement. Necrosis was defined as the presence of ill defined, irregular areas within the tumor that did not demonstrate contrast enhancement during the nephrographic and delayed phases. After nephrectomy, patients were followed with a history, physical exam, basic laboratory testing and serial imaging of the chest and abdomen every six to 12 months for at least three years based on the tumor risk group. The presence and site of metastases during follow-up were collected.

MFP was calculated from nephrectomy until diagnosis of metastases. Patients who died or were metastases free at last follow-up were censored, consistent with Raj et al. nomogram methodology. Overall survival (OS) was calculated from time of nephrectomy until death; patients alive at last follow-up were censored. Disease specific survival (DSS) was calculated from time of nephrectomy until death from disease. Patients who died of other or unknown causes, or who were alive at last follow-up were censored. MFP, OS, and DSS were estimated with Kaplan-Meier methods and plots.

Univariable Cox regression models assessed the relationship between factors included within the Raj et al. nomogram and metastasis-free probability. The linear predictor and 12-year predicted MFP from the nomogram was calculated, as visualized in Figure 1, and put into a

univariable Cox model. Model discrimination was assessed with Gonen and Heller's CPE. We also assessed discrimination with time-dependent ROC curves plotted at available years using the inverse probability of censoring weighting approach.[17] Predicted 12-year MFP was stratified into tertiles (12-year MFP = 0-33%, 33-67%, 67%-100%), and plotted with Kaplan-Meier methods to further visualize model performance. Calibration of the model was visualized with a calibration plot. For the calibration plot, patients were placed into ranked tertiles (each 1/3 of patients) of predicted 12-year MFP and the mean predicted 12-year MFP of each group was plotted against the observed Kaplan-Meier estimate.

As a sensitivity analysis, we examined the association between the linear predictor and MFP when death from other/unknown causes was treated as a competing risk. Two-sided p-values less than 0.05 were considered statistically significant. We used SAS 9.4 (The SAS Institute, Cary, NC) and the 'CPE' package[18] within Cran R Version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) for all analyses.

Results

Clinical Characteristics of the Study Cohort

The cohort included 1,760 patients with a median age of 60 years (IQR:52-69), 658 of whom (37%) were female. Most patients presented incidentally (83%, 1469/1760), 274/1760 (16%) presented with localized symptoms due to their tumor, and 17/1760 (1%) presented with systemic symptoms. On imaging, lymphadenopathy was uncommon (3%, 46/1760) and 55% of patients had necrosis (966/1760). Median tumor diameter was 3.7cm (IQR: 2.5-5.5), (Table 1).

Metastases Free Survival and Nomogram Validation

Median follow-up in non-metastatic patients (N=1594) was 7.7 years (IQR:5.3-9.7). By the end of follow-up, 166 patients had metastatic disease. Six-year MFP was 91% (89-92%) and 12-year MFP was 88% (86-90%), (Supplementary Figure 2). The most common sites of metastases included lung (49%, 82/166), bone (19%, 32/166) and lymph nodes (17%, 29/166), (Figure 2).

Age at surgery, mode of presentation, lymphadenopathy, necrosis and tumor dimension were all significant predictors of MFP on univariate analysis (Table 2). Male gender was associated with decreased MFP; however, the association did not reach statistical significance (HR:1.37, 95% CI:0.99-1.91, p=0.06).

The linear predictor from Raj et al. showed good discrimination (CPE:0.77+/- 0.01). The three probability tertiles had clearly separated MFP curves. At 12 years, MFP was 37% (21-53%) in the 1st tertile, 60% (50-69%) in the 2nd tertile, and 92% (90-94%) in the 3rd tertile (Figure 3A). While discrimination was high, calibration of the model was fair. Predicted mean survival was consistently lower than actual survival. While the highest tertile overlapped with the 45-degree reference line, the last two tertiles had minimal overlap, suggesting overestimation (Figure 3B).

The time-dependent ROC curves showed strong discrimination at all time points, however, the performance was strongest in earlier years, where the AUC for years 2 and 4 were 0.87 (95% CI:0.84-0.91) and 0.87 (95% CI:0.84-90), and decreased to 0.83 (95% CI:0.79-0.87) and 0.83 (95% CI:0.78-0.89) by years 10 and 12 (Figure 4).

Overall and Disease Specific Survival

By the end of follow-up, 277 patients had died. Six- and 12-year OS were 89% (87-91%) and 74% (71-77%), respectively. Six- and 12-year DSS estimates were 96% (95-97%) and 95% (94-97%), respectively (Supplementary Figure 3).

MFP Sensitivity Analyses

With death as a competing risk, 6- and 12-year cumulative incidence of metastases was 2.3% (1.7-3.1%) and 3.9% (3.1-4.9%), respectively (Supplementary Figure 4). The nomogram linear predictor was significantly associated with MFP using competing risks methodology (HR:3.14, 95% CI:2.72-3.63, $p<0.001$).

Discussion

Several preoperative models, based on patient and tumor characteristics on imaging, were developed to predict recurrence free and DSS in patients undergoing nephrectomy.[6-11] Model accuracy at external validation ranged from 65% - 67% for models evaluating patients with localized RCC and 78% - 88% for those evaluating patients at all stages.[9, 12, 13] However, since most of these models were published, there has been a change in the clinical characteristics of localized renal masses. The extensive use of abdominal imaging for the evaluation of other causes increased the rate of incidentally detected renal masses with a decrease in the rate of patients diagnosed with local or systemic symptoms.[15] Similarly, tumor size and stage at diagnosis decreased over time.[1, 14, 15] These changes in the landscape of renal masses question the validity of previous preoperative nomograms that were built based on non-contemporary cohorts.

Raj et al. used pooled data from the institutional databases of the Mayo Clinic and Memorial Sloan Kettering Cancer Center and developed a preoperative model to predict 12-year likelihood of metastatic recurrence among patients with localized renal masses treated with nephrectomy. In their publication, the median follow-up was 4.7 years with a MFP rate of 70% (95% CI: 68% - 72%), the concordance index of the nomogram was 0.8 and the model had good calibration.[8] The current study is the first to validate the nomogram proposed by Raj et al. Compared to the original cohort, and consistent with the reported changes in tumor characteristics at diagnosis in recent years, the current contemporary cohort had a higher rate of incidental findings (84% vs. 51%), lower rate of lymphadenopathy (2% vs. 6%) and smaller median tumor size (3.7cm vs. 5.3cm). We observed a longer follow-up (7.7 years) and a higher estimated 12-year MFP (88%) than previously reported, possibly due to a higher rate of low stage disease in the current cohort. We noted a high rate of necrosis likely related to the use of central radiology review rather than relying on imaging reports, which may have reduced the calibration of the model together with the relatively low rate of metastatic events we observed. Despite these changes in the characteristics of the cohort, the

individual predictors of the nomogram remained associated with outcome and the model demonstrated strong discrimination with a concordance index of 0.77 and a time-dependent AUC at 12 years of 0.83. Thus, the current study, performed on a large contemporary cohort with long follow-up, demonstrates the applicability of the preoperative nomogram despite the change in the clinicopathologic characteristic of RCC over time.

Neoadjuvant treatment for RCC may be beneficial by treating micro-metastatic disease and reducing tumor size making it amendable to surgery, and is expected to be better tolerated than treatment after surgery.[19] Furthermore, it has been suggested that pro-angiogenic and pro-immunogenic factors present in the primary tumor may enhance the effect of targeted therapy and immunotherapy given in the neoadjuvant setting.[20] Phase II trials evaluating the use of neoadjuvant tyrosine kinase inhibitors in patients with localized and locally advanced renal tumor have shown substantial tumor shrinkage and a decrease in nephrometry scores following treatment.[21-23] Recent phase II trials in non-small-cell lung cancer and melanoma have demonstrated the feasibility and potential benefit of neoadjuvant immunotherapy.[3, 4] Current ongoing trials are evaluating the safety and benefit of neoadjuvant immunotherapy and combination treatments of tyrosine kinase inhibitors and immune checkpoint blockade for RCC.[20] Due to the substantial rate of high-grade toxicities, especially when combining ipilimumab and nivolumab,[3] accurate preoperative risk stratification to identify high-risk patients who may be trial candidates is warranted. The current nomogram, validated on a contemporary cohort, may be suitable for this purpose. The highest risk group of patients had a metastasis free probability of 37% at years 6 and 12, most of whom recurred early. This high-risk group of patients may be most suitable for inclusion in future neoadjuvant trials while limiting the exposure of lower risk patients to neoadjuvant treatment thus avoiding the associated toxicities.

Recent studies have shown an improvement in the diagnostic accuracy of renal mass biopsy which is currently above 90%.[24] Furthermore, recurrent genomic alterations, which may be identified on renal biopsy, have been associated with pathological and clinical outcome in RCC; however, only few studies evaluated the added benefit of these alterations to commonly used prognostic models.[25-27] While an initial report did not show an increase in the predictive accuracy when adding genomic markers to a preoperative model including tumor size and age and the postoperative Mayo Clinic stage, size, grade, and necrosis (SSIGN) prognostic scoring system,[25] subsequent studies suggest *TP53*, *SETD2* and *BAP1* may have an independent prognostic role after adjusting for various postoperative models. [26, 27] Since renal mass biopsies are routinely obtained prior to inclusion in neoadjuvant trials, future studies should evaluate whether histologic and genomic data obtained from these biopsies may enhance preoperative risk stratification among patients with high risk renal tumors.

The limitations of our study include its retrospective nature which is associated with an inconsistent follow-up schedule for all patients. Although we had 8 years of follow up and over 1700 patients, due to the rarity of metastases, it would be ideal to have had a longer follow-up period. Furthermore, the relatively small number of metastatic events, most likely due to the low stage of patients included within contemporary cohorts, limit the robustness of the results and their applicability to higher risk patients; thus, additional studies are

required to validate these findings in higher risk cohorts. The focus of the current study was to validate the pre-operative model and assess whether the model performs well on an external contemporary dataset rather than assess whether additional pre-operative factors may improve prediction of outcome in patients with renal masses. Furthermore, we were unable to compare the predictive abilities of the validated nomogram to those of other pre-operative models which predict cancer-specific and recurrence-free survival rather than metastatic-free probability.

Conclusions

The current study validates our previously published preoperative nomogram in a contemporary cohort of patients, demonstrating its relevance despite the changing population of patient diagnosed with RCC. Future studies should evaluate the role of preoperative risk stratification in patient selection for neoadjuvant treatment. In addition, studies should explore whether inclusion of information obtained from pretreatment renal biopsy can improve preoperative risk prediction in this group of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Contemporary RCC patients have more incidental findings, less lymphadenopathy and smaller tumors
- Estimated 12-year metastatic-free probability was 88% for localized RCC
- Preoperative nomogram for metastatic-free probability showed strong discrimination in contemporary patients
- Preoperative nomograms may aid in patient selection for neoadjuvant treatment

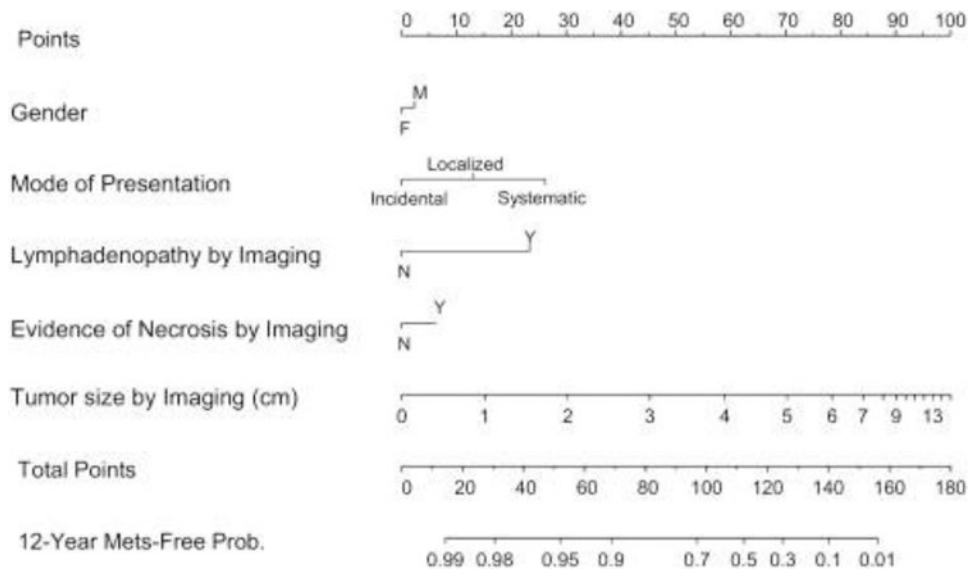


Figure 1 –. Preoperative nomogram predicting freedom from metastatic recurrence at 12 years following definitive surgical management. Obtained with permission from: Raj GV, Thompson RH, Leibovich BC, Blute ML, Russo P, Kattan MW. Preoperative nomogram predicting 12-year probability of metastatic renal cancer. *The Journal of Urology*. 2008; 179:2146-51; <https://www.auajournals.org/doi/10.1016/j.juro.2008.01.101>

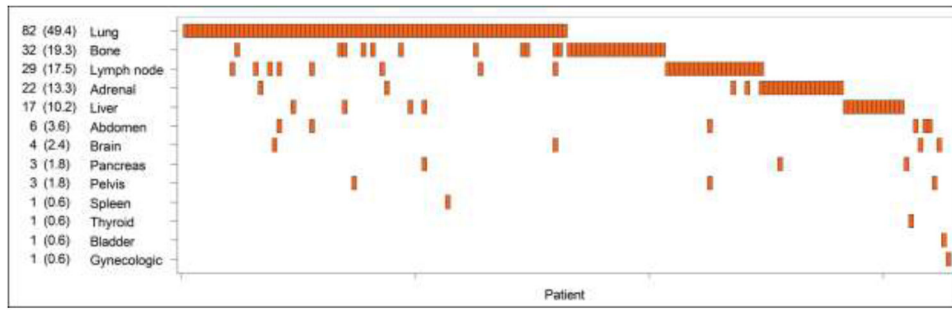


Figure 2 -
Heatmap of metastatic sites with associated frequency among the cohort (n=1,760)

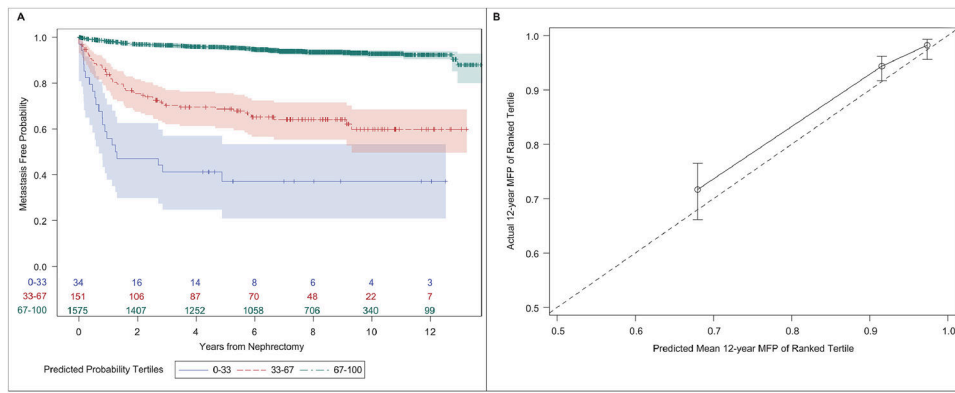


Figure 3 –. (A) Kaplan-Meier plot of metastasis-free probability stratified by tertiles of predicted 12-year metastasis-free probability in the cohort; (B) Calibration plot of the nomogram fit in the cohort of patients who underwent nephrectomy for localized renal tumor (n=1,760). The circles represent the predicted mean and actual 12-year MFS with the bars representing confidence limits around the estimate. The dashed line represents the 45-degree line

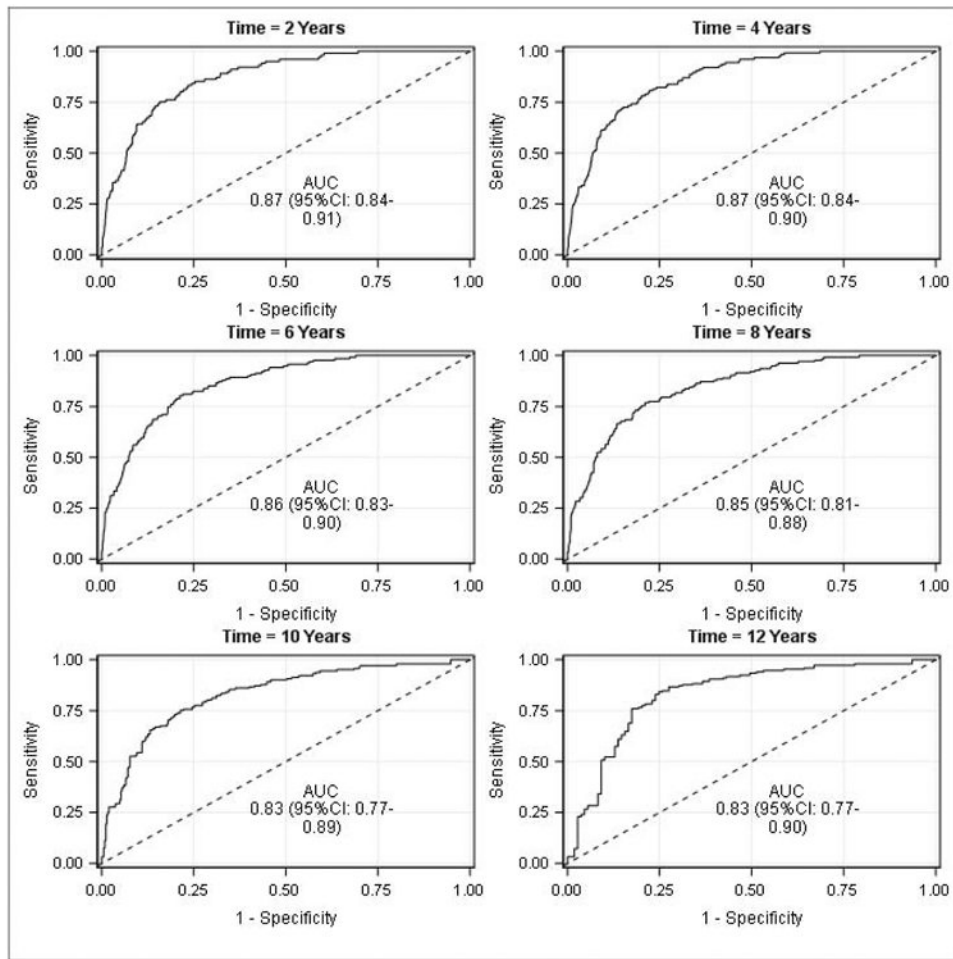


Figure 4 –.
Time-dependent ROC curves for metastasis-free probability for all patients (n=1760)

Table 1.

Clinical characteristics of the cohort (n=1,760); numbers represent frequency with percent of total in parentheses unless otherwise specified

		N (%)
Age at surgery, years	Median (IQR)	60 (52-69)
Gender	Male	1102 (63)
	Female	658 (37)
Race	White	1560 (89)
	Black	93 (5)
	Asian	63 (4)
	Other	26 (2)
	Unknown	18 (1)
Presentation	Incidental	1469 (84)
	Local	274 (16)
	Systemic	17 (1)
Lymphadenopathy	Yes	46 (3)
	No	1714 (97)
Necrosis	Yes	966 (55)
	No	794 (45)
Maximum Dimension, cm	Median (IQR)	3.7 (2.5-5.5)
ASA Score	I - II	921 (52)
	III - IV	835 (47)
	Unknown	4 (0)
Operation type	Partial Nephrectomy	1031 (59)
	Radical Nephrectomy	341 (19)
	Laparoscopic Partial Nephrectomy	193 (11)
	Laparoscopic Radical Nephrectomy	55 (3)
	Robotic Partial Nephrectomy	133 (8)
	Robotic Radical Nephrectomy	7 (0)

IQR = interquartile range; ASA = American Society of Anesthesiologists. Percentages of total may not add exactly to 100% due to rounding

Table 2.

Univariable Cox regression for preoperative predictors of metastasis-free probability included in the Raj et al. nomogram (n=1760)

		Univariable			
		N(E)	HR	[95% CI]	p-value
Age at Surgery, years		1760 (166)	1.02	[1.00 – 1.03]	0.010
Gender	Male	1102 (115)	1.37	[0.99 – 1.91]	0.06
	Female	658 (51)	REF		
Presentation	Systemic	17 (11)	19.73	[10.54 – 36.94]	<.001
	Local	274 (60)	3.75	[2.71 – 5.18]	<.001
	Incidental	1469 (95)	REF		
Lymphadenopathy	Yes	46 (20)	6.82	[4.27 - 10.90]	<.001
	No	1714 (146)	REF		
Necrosis	Yes	966 (144)	5.94	[3.79 - 9.30]	<.001
	No	794 (22)	REF		
Maximum Dimension, cm		1760 (166)	1.25	[1.22 - 1.29]	<.001

N=Total # patients for level; #E = # events for level; HR = hazard ratio; 95%CI = 95% confidence interval