available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Kidney Cancer

Prediction of Pulmonary Metastasis in Renal Cell Carcinoma Patients with Indeterminate Pulmonary Nodules

Mehrad Adibi[a], *Patrick A. Kenney*[a], *Arun Z. Thomas*[a], *Leonardo D. Borregales*[a], *Graciela M. Nogueras-González*[b], *Xuemei Wang*[b], *Catherine E. Devine*[c], *Jose A. Karam*[a], *Christopher G. Wood*[a,*]

[a] *Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [b] *Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [c] *Department of Radiology, University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Article info

Article history:
Accepted August 29, 2015

Associate Editor:
Giacomo Novara

Keywords:
Prognosis
Pulmonary nodules
Renal cell carcinoma

Abstract

Background: Indeterminate pulmonary nodules (IPN) are of uncertain significance in patients with renal cell carcinoma.
Objective: We sought to determine predictors of IPN progression to pulmonary metastasis and develop a tool for individualized risk stratification of patients who present with IPN on preoperative chest imaging in the setting of localized or locally advanced renal cell carcinoma.
Design, setting, and participants: We reviewed all patients who had radical nephrectomy with no evidence of distant metastases at a single institution from 2005–2009 who had $\geq$1 IPN on chest computed tomography that measured $<$2 cm. All chest computed tomographies were rereviewed by a radiologist who was blinded to outcomes, to independently determine number, size, and location of nodules.
Outcome measurements and statistical analysis: The primary objective of the study was to develop a prognostic model to predict pulmonary metastases among radical nephrectomy patients who present with IPN based on readily available preoperative imaging and postoperative pathological criteria. Univariable and multivariable Cox regression models were used to assess the predictive factors for development of pulmonary metastasis. We developed a nomogram that predicted the 3-yr and 5-yr lung metastasis-free survival (LMFS), with assessment of discrimination and internal validation.
Results and limitations: Among 251 patients with IPN who underwent nephrectomy, 72 (29%) developed pulmonary metastases. Median follow-up for the cohort was 36.6 mo. Three-yr and 5-yr probability of LMFS for the overall cohort was 71% (95% confidence interval 65–77%) and 65% (95% confidence interval 57–72%), respectively. The nomogram developed included number and size of IPN along with postoperative pathological variables, and showed calibration with a concordance index (c-index) of 0.81 and a bootstrap corrected c-index of 0.78. Limitations include retrospective study with no external validation.
Conclusions: We developed a nomogram to predict the individualized risk LMFS for patients who underwent nephrectomy for localized or locally advanced renal cell carcinoma.
Patient summary: We reviewed outcomes among kidney cancer patients who presented with small lung nodules and developed a clinical tool to predict risk of developing lung metastases.

* Corresponding author. University of Texas MD Anderson Cancer Center, Department of Urology 1515 Holcombe Boulevard, Unit 1373, Houston, TX 77030-4009, USA. Tel. +1 713 792-3250; Fax: +1 713-794-4824.
E-mail address: CGWood@mdanderson.org (C.G. Wood).

http://dx.doi.org/10.1016/j.eururo.2015.08.053
0302-2838/

1. Introduction

Among patients diagnosed with renal cell carcinoma (RCC), 20–30% present with synchronous metastatic disease after nephrectomy for clinically localized renal masses [1,2]. The most common site of metastasis in patients with RCC is the lung, with an incidence of 45–75% [3]. An often-encountered clinical dilemma is the management of patients who present with localized or locally advanced RCC and have concomitant indeterminate pulmonary nodules (IPN) on preoperative chest imaging. According to published guidelines for the management of pulmonary nodules by the Fleischner Society, an IPN is a 1 mm to 3 cm round pulmonary opacity that may be benign or malignant in origin [4]. Although, per these guidelines, the majority of subcentimeter nodules are more likely to be benign, the Fleischner criteria do not apply to patients with a history of malignancy. Few prior studies have evaluated the significance of IPN in RCC patients [5–7], and are limited by small sample size, clinically heterogeneous cohorts, or lack of individualized predictive capacity.

In this study, we sought to determine predictors of progression of an IPN to pulmonary metastasis and to develop a tool for individualized risk prediction of patients who present with IPN on preoperative chest imaging in the setting of localized or locally advanced RCC.

2. Methods

2.1. Patient population

After institutional review board approval was obtained, the MD Anderson Cancer Center renal cancer database was retrospectively queried over a 5-yr period from 2005 to 2009 and identified 355 patients who underwent radical nephrectomy for RCC and had IPN confirmed with a preoperative chest computed tomography (CT) scan at presentation. An IPN was defined as a lung nodule measuring less than 2 cm on CT chest. This timeframe was chosen to allow for at least a 3-yr average follow-up period for our cohort. We included patients who had a chest CT no more than 6 mo prior to the date of surgery, had $\geq$1 IPN on imaging, and had at least one postoperative chest CT at the time of last follow-up. A prespecified IPN largest diameter cutpoint of $<$2 cm was chosen to minimize the chances of capturing patients with pre-existing primary or secondary malignancies or concurrent active pulmonary disease. The type of preoperative imaging with chest CT or chest X-ray (CXR) was at the discretion of the treating physician, but in general, patients with large and locally advanced masses or higher clinical stage preferentially underwent imaging with chest CT. We excluded 63 patients with evidence of metastatic disease at presentation, 13 patients with benign renal pathology, 15 patients with history of documented active pulmonary disease or malignancy, eight patients with unknown metastatic status, and five patients with a lung nodule $\geq$2 cm. A total of 251 patients were therefore included in the study. None of these patients underwent neoadjuvant systemic therapy. Baseline patient characteristics and pathological variables were collected. All nephrectomy specimens were reviewed by genitourinary pathologists and staged according to 2010 American Joint Committee on Cancer criteria [8]. All patients were followed postoperatively with a baseline chest and abdominal CT at 6 wk and then every 3–6 mo thereafter with repeat chest CT or CXR as indicated. Patients who developed lung metastases were treated with observation, systemic targeted therapy, metastasectomy, or a combination thereof, depending on patient and clinical characteristics.

2.2. Radiologic evaluation

Staging and follow-up chest CT and CXR of all patients meeting the inclusion criteria were rereviewed by an experienced radiologist who was blinded to outcomes. Development of pulmonary metastases was defined as a documented increase in the size or number of pulmonary lesions according to Response Evaluation Criteria In Solid Tumors criteria or a histological diagnosis of malignancy in the setting of a primary renal tumor, as reported in prior studies [5]. Patients were then classified into two groups (yes/no), based on the development of pulmonary metastases.

2.3. Statistical analysis

The primary objective of the study was to develop a prognostic model to predict pulmonary metastases among radical nephrectomy patients who present with IPN based on readily available preoperative imaging and postoperative pathological criteria. The secondary objective was to compare disease-specific survival (DSS) among patients who did and did not develop pulmonary metastases and determine predictors of DSS among the two groups. Wilcoxon rank-sum test and Pearson's Chi-square (or Fisher's exact) were used to determined differences between groups. Lung metastasis-free survival (LMFS) was calculated as the number of months from surgery to pulmonary metastasis diagnosis on postoperative CT chest or last follow-up date. Patients who were alive without pulmonary metastasis at their last follow-up were censored on that date. DSS was calculated as the number of months from surgery to death from disease or last follow-up date. Patients who were alive or dead from other disease at their last follow-up were censored on that date. The Kaplan-Meier product limit method was used to estimate the median LMFS for each clinical/demographic factor. Univariable and multivariable Cox proportional hazards regression models were used to assess the association between each of the variables and LMFS. For the multivariable analysis model, we decided to include preoperative imaging and postoperative pathological variables that were statistically significant on univariable analysis. In addition, to adjust for the potential confounding effect due to smoking, the multivariable model was fit where smoking status was included as a covariate. Similar analyses were performed for DSS.

A nomogram was developed based on the fitted multivariable Cox proportional hazards model for prediction of 3-yr and 5-yr LMFS probabilities. The nomogram was assessed for calibration and discrimination. Calibration was assessed graphically with plots of the predicted probability of LMFS at 3 yr versus the actual proportion of patients without lung metastasis at 3 yr. Patients were grouped by their nomogram-predicted probabilities and then the group means were compared with the Kaplan-Meier estimates of LMFS. Bootstrapping was used for bias correction. We assessed discrimination by the concordance index (c-index), defined as the proportion of all usable patient pairs in which the predictions and outcomes are concordant [9]. In order to adjust for the bias associated with evaluating the performance of a nomogram on the same group of patients used to build the nomogram, bootstrapping was again used for bias correction (n = 500 bootstrap samples). Specifically, random samples with the same sample size as original cohort were drawn from the original data set with replacement. After that, the same Cox model that had been derived from the original cohort was fit to the bootstrap sample. Repeating this process 500 times would produce 500 bootstrapping-based model performance indices (eg, concordance indices). The average value of these 500 performance indices is considered as the bias-corrected estimate, which would provide an estimate of the performance of the nomogram that could be expected in a separate but similar patient population. Statistical analysis was performed using STATA/SE version 13.1 statistical software (Stata Corp. LP, College Station, TX, USA) and R software version 3.1.1 (The R

Foundation for Statistical Computing). All analyses were two sided with a p-value < 0.05 considered statistically significant.

3. Results

3.1. Patient characteristics

Among 251 patients who underwent radical nephrectomy and initially presented with IPN, 72 (29%) developed pulmonary metastasis and 179 (71%) patients did not develop pulmonary metastasis at the time of last follow-up (Table 1). Patients who developed pulmonary metastases had an overall higher pathologic T stage and N stage, grade, lymphovascular invasion, and sarcomatoid component (Table 2). The pulmonary metastasis group included a higher proportion of patients with renal vein or inferior vena caval tumor thrombi and tumor fat invasion. Based on preoperative imaging characteristics (Table 3), both size and number of nodules were higher in the group with pulmonary metastases.

Table 1 – Patients characteristics

	All patients		Pulmonary metastasis development				p value
			No		Yes		
Age at surgery							0.7
N	251		179		72		
Median (IQR)	64.1 (54.1–71.3)		64.3 (53.9–71.5)		63.9 (54.3–69.8)		
BMI							0.5
N	251		179		72		
Median (IQR)	28.8 (25.3–38.8)		28.9 (25.4–33.0)		28.7 (24.7–32.4)		
Largest tumor diameter (cm)							<0.001
N	251		179		72		
Median (IQR)	8.0 (5.2–10.4)		7.3 (4.6–9.5)		9.5 (7.0–11.2)		
Creatinine							0.002
N	250		179		71		
Median (IQR)	1.1(0.9–1.3)		1 (0.9–1.2)		1.2 (1.0–1.4)		
Albumin							0.5
N	187		136		51		
Median (IQR)	4.2 (4.0–4.5)		4.2 (4.0–4.5)		4.3 (3.8–4.6)		
LDH							0.08
N	223		158		65		
Median (IQR)	456.0 (389–553)		471.5 (399–557)		426 (377–508)		
Hemoglobin							0.002
N	249		179		70		
Median (IQR)	13.3 (12.1–14.2)		13.4 (12.7–14.5)		12.9 (11.4–13.9)		
Calcium							0.2
N	198		143		55		
Median (IQR)	9.4 (9.1–9.7)		9.4 (9.1–9.8)		9.5 (9.2–9.7)		
	N	%	*N*	%	*N*	%	
Sexr							0.06
Male	159	63	107	59	52	72	
Female	92	37	72	41	20	28	
Race							0.9
White	202	81	144	80	58	81	
Other	49	19	35	20	14	19	
ASA							0.14
2	61	24	48	27	13	18	
>2	190	76	131	73	59	82	
Smoker							0.8
No	106	42	75	42	31	43	
Yes	145	58	104	58	41	57	
ECOG							0.002
0	76	30	65	36	11	15	
1	165	66	106	59	59	82	
>1	10	4	8	5	2	3	
Charlson score (not age-adjusted)							0.08
0–2	118		92	51	26	36	
3–5	114		73	41	41	57	
≥6	19		14	8	5	7	
Symptomatic presentation							<0.001
No	112	45	93	52	19	26	
Yes	139	55	86	48	53	74	
Respiratory symptoms							0.002
No	233	93	172	96	61	85	
Yes	18	7	7	4	11	15	

ASA = American Society of Anesthesiologists; IQR = interquartile range; LDH = lactate dehydrogenase.

Table 2 – Pathological characteristics

	All patients		Pulmonary metastasis development				*p* value
			No		Yes		
	N	%	*N*	%	*N*	%	
Pathologic T stage							<0.001
pT1/T2	95	38	86	48	9	13	
pT3/ T4	156	62	93	52	63	87	
Pathologic N stage							<0.001
p N0	112	45	68	38	44	61	
p N1	13	5	6	3	7	10	
p Nx	126	50	105	59	21	29	
Fuhrman grade							<0.001
G1-G2	65	26	62	36	3	4	
G3-G4	181	74	112	64	69	96	
Histology							0.03
Clear-cell	201	80	137	77	64	89	
Non clear-cell	50	20	42	23	8	11	
LVI							0.003
No	220	88	164	92	56	78	
Yes	31	12	15	8	16	22	
Sarcomatoid							<0.001
No	235	94	174	97.2	61	85	
Yes	16	6	5	2.8	11	15	
Venous tumor thrombus							<0.001
None	154	61	128	72	26	36	
Renal vein	48	19	33	18	15	21	
IVC below diaphragm	44	18	17	9	27	38	
IVC above diaphragm	5	2	1	1	4	5	
Fat invasion							<0.001
No	108	43	95	53	13	18	
Yes	143	57	84	47	59	82	

IVC = intravenous cholangiogram; LVI = lymphovascular invasion.

3.2. Prediction of lung metastasis and DSS

Median follow-up time was 36.6 mo (interquartile range 25.8–51.8 mo) for the entire cohort, 38.0 mo (interquartile range 25.8–51.8 mo) for patients who did not develop pulmonary metastasis, and 35.3 mo (18.7–47.2 mo) for those who did. Overall, 61 patients were dead at last follow-up, with 38 patients dead due to metastatic renal cancer. Twenty-eight of the 72 patients (39%) had biopsy-proven renal cell carcinoma in the lungs, with 36 of 72 of the largest metastatic lesions (49%) present at the same location as the largest pulmonary nodule on preoperative chest CT.

The 3-yr and 5-yr probability of LMFS for the overall cohort was 71% (95% confidence interval [CI] 65–77%) and 65% (95% CI 57–72%), respectively. Results of the univariable and multivariable analysis are shown in Table 4. A similar multivariable analysis was carried out for DSS where only the presence of fat invasion (hazards ratio [HR] 19.1, 95% CI 2.5–148.9, $p = 0.005$) was significantly associated with increased risk of kidney cancer-related mortality. Neither the number nor size of nodules remained a significant factor in predicting death from kidney cancer. The 3-yr and 5-yr DSS for the entire cohort were 86% (95% CI 81–90%) and 79% (95% CI 73–85), respectively.

3.3. Nomogram development and internal validation

Figure 1 shows the nomogram for predicting the probability of LMFS at 3-yr and 5-yr. Figure 2 shows the calibration plot of the predicted probability of LMFS at 3-yr versus the actual proportion of patients who survived 3-yr without lung metastasis. The nomogram demonstrated better calibration for patients with 3-yr LMFS probability in the range of 50–80%, with a gradual small increase in the overestimation of predicted to actual survival probabilities with 3-yr probabilities of less than 50%. The c-index and bootstrap-corrected c-index for this nomogram demonstrated good discrimination at 0.81 and 0.78, respectively (Table 5).

4. Discussion

For patients diagnosed with a localized or locally advanced renal mass in the absence of clinically confirmed distant metastatic disease who present with IPN on staging CT chest, the question often arises as to whether the pulmonary nodules represent true RCC metastasis or a primary pulmonary process. Although the preoperative detection of IPN may not deter or change the initial clinical management of these patients, the ability to predict which patients are at higher risk for development of pulmonary

Table 3 – Radiologic characteristics on chest computed tomography

	All patients		Pulmonary metastasis development				*p* value
			No		Yes		
Number of nodules on CT							<0.001
N	250		178		72		
Median (IQR)	3.0 (2–6)		3 (2–5)		4 (3–7)		
Size of nodules on CT (mm)							<0.001
N	250		178		72		
Median (IQR)	4.0 (3–6)		4 (3–5)		5 (3–7)		
D from chest CT to surgery							0.4
N	250		178		72		
Median (IQR)	18.0 (8–29)		18 (8–29)		15 (7.5–27)		
Days from CXR to surgery							0.7
N	227		160		67		
Median (IQR)	15.0 (8–26)		15 (7.5-26)		17 (8–26)		
	N	%	*N*	%	*N*	%	
Preoperative CXR							0.4
No	24	10	19	11	5	7	
Yes	227	90	160	89	67	93	
Metastasis at same location as largest Pulmonary nodule							0.5
No	37	51	2	100	35	49	
Yes	36	49	0	0	36	51	
Location of largest nodule							0.6
LLL	48	19	37	21	11	14	
LUL	51	21	34	19	17	24	
RLL	58	23	38	21	20	28	
RML	28	11	21	12	7	10	
RUL	65	26	48	27	17	24	
Nodule calcification							0.6
No	150	60	105	59	45	63	
Yes	100	40	73	41	27	37	
Pleural effusion							0.5
No	239	96	171	96	68	94	
Yes	11	4	7	4	4	6	

C = computed tomography; XR = chest X-ray; IQR = interquartile range.

metastasis may alter risk stratification, change future surveillance regimens, and potentially open the door for consideration of adjuvant therapies. To our knowledge, no clinical predictive tool currently exists for individualized prediction of progression to pulmonary metastasis in this specific patient population.

In this study, we sought to determine predictors of progression to pulmonary metastasis and develop a nomogram for individualized risk prediction in patients who present with preoperative IPN in the setting of localized or locally advanced RCC. With regards to the individual variables in the nomogram, a higher number of nodules and larger nodule size appeared to be associated with a lower LMFS. Although this finding is consistent with several studies examining IPN in the setting of colorectal cancers [10–12], it has not been studied in detail with regards to RCC. A study investigating the relation between presence of IPN and RCC progression did not find an association between presence of multiple nodules and progression to lung metastasis or death from kidney cancer, however, it did establish a higher risk of progression to any distant metastasis in the presence of multiple nodules [7]. Nevertheless, the actual number of IPN was not categorized in this study, as patients were stratified into single or multiple pulmonary nodules.

Smoking status was also included in the nomogram. Although the absence of smoking history indicating a higher risk of developing pulmonary metastasis appears counter-intuitive, this can be explained by the fact that patients who smoke have a higher chance of developing primary pulmonary diseases, including primary pulmonary malignancy which may increase the risk of presence of IPN. However these IPN may not necessarily be related to the development of pulmonary metastases due to RCC. Similarly, nodal stage was also a significant factor included in the model, as the evidence for disease progression and poorer survival in patients with node-positive disease is abundant [13,14]. Patients with N0 disease yield a higher number of points in the nomogram compared with the reference Nx. Among 144 patients who underwent concomitant lymph node dissection at the time of radical nephrectomy due to clinical suspicion of lymphadenopathy, 111 were classified as pN0. It is possible that some patients may have resulted in a false negative, thus increasing their risk for developing pulmonary metastasis. In addition, patients with pNx may have been lower risk in general due to the absence of clinical suspicion of lymphadenopathy compared to the N0 and N1 categories.

In the first study evaluating the prognostic significance of IPN in RCC, Xu et al [6] retrospectively reviewed 240 RCC

Table 4 – Univariable and multivariable analysis for lung metastasis-free survival

	Univariable analysis			Multivariable analysis		
	HR	95% CI for HR	*p* value	HR	95% CI for HR	*p* value
Largest tumor diameter (cm)	1.12	(1.06–1.18)	<0.001	1.01	(0.94–1.09)	0.8
Number of nodules on CT	1.15	(1.08–1.23)	<0.001	1.11	(1.03–1.19)	0.004
Size of nodules on CT (mm)	1.27	(1.16–1.39)	<0.001	1.17	(1.05–1.30)	0.006
Smoker						
No	Ref			Ref		
Yes	1.01	(0.64–1.62)	0.9	0.82	(0.50–1.35)	0.4
Charlson score (not age-adjusted)						
0–2	Ref					
3-5	1.80	(1.10–2.95)	0.02			
≥6	1.67	(0.64–4.36)	0.3			
ECOG						
0	Ref					
1	3.04	(1.59–5.79)	0.001			
>1	1.94	(0.43–8.81)	0.4			
T stage						
T1/T2	Ref					
T3/T4	5.45	(2.71–10.98)	<0.001			
N stage						
N0	Ref			Ref		
N1	2.21	(0.99–4.96)	0.053	1.38	(0.60–3.21)	0.5
Nx	0.35	(0.21–0.58)	<0.001	0.57	(0.32–1.02)	0.057
Fuhrman grade						
G1–G2	Ref			Ref		
G3–G4	9.71	(3.06–30.85)	<0.001	4.88	(1.48–16.10)	0.009
Histology						
Clear-cell	Ref					
Non clear-cell	0.49	(0.23–1.01)	0.054			
LVI						
No	Ref					
Yes	3.09	(1.77–5.40)	<0.001			
Sarcomatoid						
No	Ref			Ref		
Yes	4.59	(2.28–8.30)	<0.001	2.23	(1.06–4.70)	0.03
Venous tumor thrombus						
None	Ref	(1.02–3.65)	0.043	Ref	(0.49–1.92)	0.9
Renal vein	1.93	(3.48–10.37)	<0.001	0.97	(1.17–4.15)	0.01
IVC below diaphragm	6.01	(3.23–27.17)	<0.001	2.20	(0.68–8.53)	0.2
IVC above diaphragm	9.37	(1.02–3.65)	0.043	2.40	(0.49–1.92)	0.9
Fat invasion						
No	Ref					
Yes	4.59	(2.51–8.39)	<0.001	2.05	1.01–4.14	0.046
Location of largest nodule						
LLL	Ref					
LUL	1.53	(0.71–3.26)	0.3			
RLL	1.53	(0.73–3.19)	0.3			
RML	1.10	(0.43–2.85)	0.8			
RUL	1.21	(0.57–2.59)	0.6			
Pleural effusion						
No	Ref					
Yes	1.29	(0.47–3.54)	0.6			

CI = confidence interval; CT = computed tomography; HR = hazards ratio; IVC = intravenous cholangiogram; LVI = lymphovascular invasion; Ref = reference value.

patients, among which 92 presented with IPN on initial chest CT. Although this study compared the outcomes of patients with and without IPN to identify prognostic factors for disease progression, their subanalysis of the IPN group did not yield any significant results, likely due to small numbers in the IPN cohort. In contrast, our study evaluates a larger group of patients, all of whom initially present with IPN, and compares outcomes among those who did and did not develop pulmonary metastasis. A more recent study evaluating IPN in RCC resulted in significantly different conclusions. Mano et al [7] reported the results of 748 patients with RCC, of which 382 patients presented with IPN, over a 10-yr period and median follow-up of 4 yr. They stratified their results by IPN size (≤1 cm vs >1 cm) and number (one vs multiple). In the final multivariable analysis, after adjusting for stage, tumor size, and histology among the 382 patients presenting with IPN, nodule size >1 cm was significantly associated with both development of lung metastasis (HR 3.6, 95%CI 1.6–8.3, $p = 0.002$) and any distant metastasis (HR 2.5, 95%CI 1.1–5.7, $p = 0.03$)

Table 5 – Univariable and multivariable analysis for disease-specific survival

	Univariable analysis			Multivariable analysis		
	HR	95% CI for HR	*p* value	HR	95% CI for HR	*p* value
Largest tumor diameter (cm)	1.15	(1.07–1.25)	<0.001	1.03	(0.90–1.16)	0.7
Number of nodules on CT	1.17	(1.08–1.26)	<0.001	1.09	(0.99–1.19)	0.07
Size of nodules on CT (mm)	1.27	(1.13–1.43)	<0.001	1.14	(0.99–1.32)	0.07
Smoker						
No	Ref			Ref		
Yes	1.47	(0.75–2.87)	0.3	1.37	(0.67–2.81)	0.4
Charlson score (not age–adjusted)						
0–2	Ref					
3–5	2.08	(1.03–4.20)	0.04			
≥6	4.05	(1.29–12.71)	0.02			
ECOG						
0	Ref					
1	5.90	(1.81–19.28)	0.003			
>1	13.58	(2.70–68.21)	0.002			
T stage						
T1/T2	Ref					
T3/T4	24.69	(3.39–180.06)	0.002			
N stage						
N0	Ref			Ref		
N1	2.87	(1.08–7.63)	0.03	1.98	(0.67–5.88)	0.2
Nx	0.48	(0.23–0.97)	0.04	1.23	(0.56–2.69)	0.6
Fuhrman grade						
G1–G2	Ref			Ref		
G3–G4	12.84	(1.76–93.61)	0.01	4.53	(0.59–34.84)	0.15
Histology						
Clear–cell	Ref					
Non clear–cell	1.19	(0.54–2.59)	0.7			
LVI						
No	Ref					
Yes	5.69	(2.97–10.92)	<0.001			
Sarcomatoid						
No	Ref			Ref		
Yes	2.08	(0.74–5.88)	0.16	0.76	(0.24–2.46)	0.6
Venous tumor thrombus						
None	Ref			Ref		
Renal vein	1.48	(0.56–3.96)	0.4	0.56	(0.20–1.54)	0.3
IVC below diaphragm	6.30	(3.00–13.21)	<0.001	1.65	(0.71–3.86)	0.2
IVC above diaphragm	9.29	(2.60–33.23)	0.001	2.71	(0.60–12.15)	0.2
Fat invasion						
None	Ref			Ref		
Yes	32.14	(4.41–234.45)	0.001	19.14	(2.46–148.91)	0.005
Location of largest nodule						
LLL	Ref					
LUL	1.15	(0.51–2.63)	0.7			
RLL	0.53	(0.20–1.38)	0.2			
RML	0.32	(0.07–1.47)	0.14			
RUL	0.44	(0.16–1.21)	0.11			
Pleural effusion						
No	Ref					
Yes	2.39	(0.85–6.75)	0.09			

CI = confidence interval; CT = computed tomography; HR = hazards ratio; IVC = intravenous cholangiogram; LVI = lymphovascular invasion; Ref = reference value.

compared with patients with IPN ≤1 cm. However, among patients presenting with IPN, number of nodules was not a significant predictor of any distant metastasis. Similarly, we excluded patients with IPN >2 cm in size and our results also indicate that size and number of nodules are associated with LMFS and are not associated with DSS; however, our study results did not indicate a size cutoff for the largest pulmonary nodule, but rather incorporated the actual number and size of nodules present as a continuous variable. As a result, while in the Mano et al [7] study, nodules greater than 1 cm in size were significantly associated with development of lung and distant metastases compared to those with no IPN, we found that a continuous increase in nodule size and number result in progressively incremental risk of developing pulmonary metastasis.

The current study has some limitations. This is a retrospective single-institutional study with inherent selection bias. Also, there was a lack of standardized preoperative and postoperative imaging strategy. In addition, heterogeneous medical and surgical treatment of patients diagnosed with pulmonary metastasis may alter

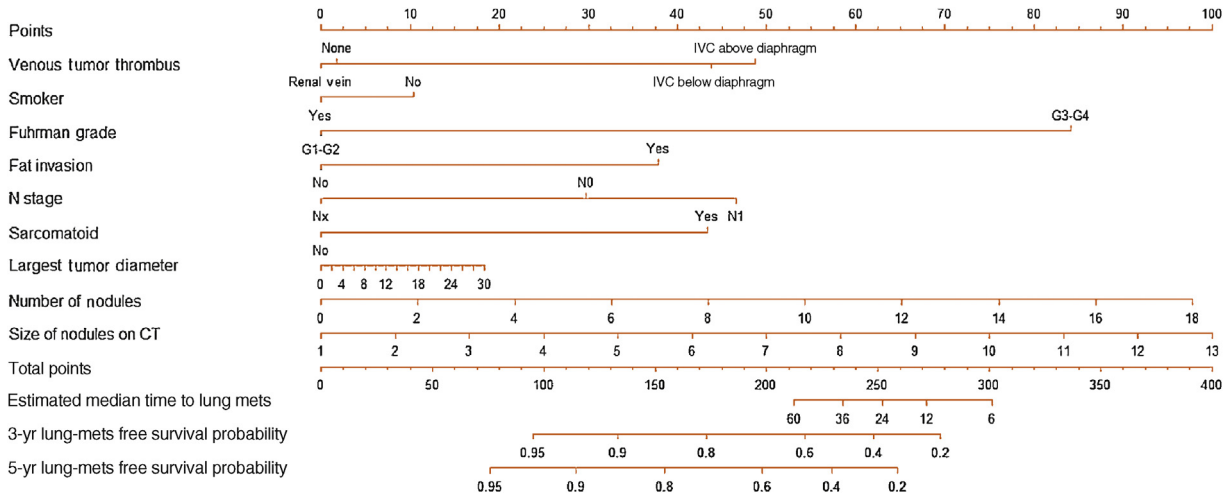

Fig. 1 – Nomogram for lung metastasis-free survival at 3 yr and 5 yr, as well as the median lung metastasis-free survival based on the fitted Cox model. CT = computed tomography; IVC = intravenous cholangiogram.

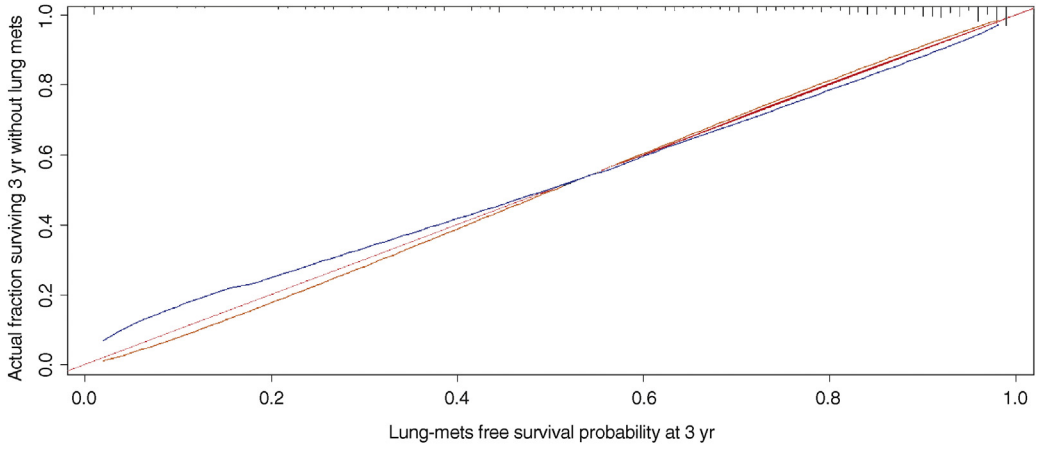

Fig. 2 – Calibration of the nomogram.
Mets = metasis.

the DSS. Also, improved imaging techniques during the 4-yr timespan of the study may have altered the detection rate of IPN. Despite these limitations, our individualized predictive tool can be used in the clinical setting to create a framework for more frequent follow-up, earlier detection, and possible treatment of pulmonary metastases. However, further multi-institutional studies are necessary to externally validate the nomogram in a larger cohort of patients.

5. Conclusions

We developed a nomogram to predict the individualized risk of LMFS for patients presenting with IPN <2 cm on chest CT among a cohort of patients who presented with localized or locally advanced RCC.

Author contributions: Christopher G. Wood had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Adibi, Kenney.
Acquisition of data: Kenney, Devine.
Analysis and interpretation of data: Adibi, Thomas, Borregales.
Drafting of the manuscript: Adibi.
Critical revision of the manuscript for important intellectual content: Thomas, Borregales, Wood, Karam, Devine, Kenney.
Statistical analysis: Nogueras-González, Wang.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Wood.
Other: None.

Financial disclosures: Christopher G. Wood certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** Supported in part by the Cancer Center Support Grant for Biostatistics (NCI Grant P30 CA016672).

References

[1] Flanigan RC, Campbell SC, Clark JI, Picken MM. Metastatic renal cell carcinoma. Curr Treat Options Oncol 2003;4:385–90.

[2] Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 2001;358:966–70.

[3] Bianchi M, Sun M, Jeldres C, Shariat SF, Trinh QD, Briganti A, et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. Ann Oncol 2012;23:973–80.

[4] MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology 2005;237:395–400.

[5] Hanamiya M, Aoki T, Yamashita Y, Kawanami S, Korogi Y. Frequency and significance of pulmonary nodules on thin-section CT in patients with extrapulmonary malignant neoplasms. Eur J Radiol 2012;81:152–7.

[6] Xu R, Horick N, McGovern FJ, Dahl DM, Feldman AS, Blute ML, et al. Prognostic significance of indeterminate lung nodules in renal cell carcinoma. Urol Oncol 2014;32:355–61.

[7] Mano R, Vertosick E, Sankin AI, Chevinsky MS, Larish Y, Jakubowski CD, et al. Subcentimeter pulmonary nodules are not associated with disease progression in patients with renal cell carcinoma. J Urol 2015;193:776–82.

[8] Edge Sea. American Joint Committee on Cancer., American Cancer Society. AJCC cancer staging handbook: from the AJCC cancer staging manual. New York: Springer; 2010.

[9] Harrell Jr F, Lee K, Mark D. Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15: 361–87.

[10] Quyn AJ, Matthews A, Daniel T, Amin AI, Yalamarthi S. The clinical significance of radiologically detected indeterminate pulmonary nodules in colorectal cancer. Colorectal Dis 2012;14:828–31.

[11] Varol Y, Varol U, Karaca B, Karabulut B, Sezgin C, Uslu R. The frequency and significance of radiologically detected indeterminate pulmonary nodules in patients with colorectal cancer. Med Princ Pract 2012;21:457–61.

[12] Kim CH, Huh JW, Kim HR, Kim YJ. Indeterminate pulmonary nodules in colorectal cancer: follow-up guidelines based on a risk predictive model. Ann Surg 2015;261:1145–52.

[13] Ward JF, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. The influence of pNx/pN0 grouping in a multivariate setting for outcome modeling in patients with clear cell renal cell carcinoma. J Urol 2002;168:56–60.

[14] Pantuck AJ, Zisman A, Dorey F, Chao DH, Han KR, Said J, et al. Renal cell carcinoma with retroperitoneal lymph nodes: role of lymph node dissection. J Urol 2003;169:2076–83.