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European Association of Urology

Platinum Priority
Editorial by XXX on pp. x–y of this issue

A Clinical Decision Aid to Support Personalized Treatment Selection for Patients with Clinical T1 Renal Masses: Results from a Multi-institutional Competing-risks Analysis

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Article info

Article history:
Accepted November 1, 2021

Associate Editor:
James Catto

Statistical Editor:
Andrew Vickers

Keywords:
Renal cell carcinoma
Decision aid
Comorbidity
Performance status
Treatment
Nephrectomy
Ablation
Surveillance
Shared decision-making
Competing risks

Abstract

Background: Personalized treatment for clinical T1 renal cortical masses (RCMs) should take into account competing risks related to tumor and patient characteristics.
Objective: To develop treatment-specific prediction models for cancer-specific mortality (CSM), other-cause mortality (OCM), and 90-d Clavien grade ≥3 complications across radical nephrectomy (RN), partial nephrectomy (PN), thermal ablation (TA), and active surveillance (AS).
Design, setting, and participants: Pretreatment clinical and radiological features were collected for consecutive adult patients treated with initial RN, PN, TA, or AS for RCMs at four high-volume referral centers (2000–2019).
Outcome measurements and statistical analysis: Prediction models used competing-risks regression for CSM and OCM and logistic regression for 90-d Clavien grade ≥3 complications. Performance was assessed using bootstrap validation.
Results and limitations: The cohort comprised 5300 patients treated with RN (n = 1277), PN (n = 2967), TA (n = 476), or AS (n = 580). Over median follow-up of 5.2 yr (interquartile range 2.5–8.7), there were 117 CSM, 607 OCM, and 198 complication events. The C index for the predictive models was 0.80 for CSM, 0.77 for OCM, and 0.64 for complications. Predictions from the fitted models are provided in an online calculator (https://small-renal-mass-risk-calculator.fredhutch.org). To illustrate, a hypothetical 74-yr-old male with a 4.5-cm RCM, body mass index of 32 kg/m^2, estimated glomerular filtration rate of 50 ml/min, Eastern Cooperative Oncology Group performance status of 3, and

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https://doi.org/10.1016/j.eururo.2021.11.002

Please cite this article as: S.P. Psutka, R. Gulati, Michael A.S. Jewett et al., A Clinical Decision Aid to Support Personalized Treatment Selection for Patients with Clinical T1 Renal Masses: Results from a Multi-institutional Competing-risks Analysis, Eur Urol (2021), https://doi.org/10.1016/j.eururo.2021.11.002

Charlson comorbidity index of 3 has predicted 5-yr CSM of 2.9–5.6% across treatments, but 5-yr OCM of 29% and risk of 90-d Clavien grade 3–5 complications of 1.9% for RN, 5.8% for PN, and 3.6% for TA. Limitations include selection bias, heterogeneity in practice across treatment sites and the study time period, and lack of control for surgeon/hospital volume.

Conclusions: We present a risk calculator incorporating pretreatment features to estimate treatment-specific competing risks of mortality and complications for use during shared decision-making and personalized treatment selection for RCMs.

Patient summary: We present a risk calculator that generates personalized estimates of the risks of death from cancer or other causes and of complications for surgical, ablation, and surveillance treatment options for patients with stage 1 kidney tumors.

1. Introduction

Patients with clinical T1 renal cortical masses (RCMs) may be offered up to four treatment options: radical nephrectomy (RN), partial nephrectomy (PN), thermal ablation (TA), or active surveillance (AS) [1–4]. While RN was traditionally considered the gold standard for the management of all renal masses, recent guidelines recommend PN as the preferred treatment modality when feasible to maximally preserve renal function, acknowledging the slight increase in the complication profile with a nephron-sparing approach [3]. Treatment selection must balance the competing risks associated with the tumor against those related to the patient's health, including comorbidities and performance status. This calculus is complex and involves substantial uncertainty, with few validated tools available to assist in quantifying the trade-offs for different therapeutic approaches. Currently, the majority of patients with RCMs are treated operatively, and concern exists over the limited adoption of AS and the potential for overtreatment, especially among older and medically complex patients [5]. Furthermore, to the best of our knowledge there are no tools that compare treatment-specific cancer-specific mortality (CSM) and other-cause mortality (OCM) as well as treatment-specific morbidity. In this era of personalized medicine, understanding the role of comorbid conditions, age, and treatment-associated quality-of-life outcomes is imperative when designating appropriate treatment options for patients with localized RCMs.

Conventionally, more aggressive interventions are preferentially offered to young, healthy patients on the basis of their generally long life expectancy and the low likelihood of cure with adjuvant or salvage therapies for advanced renal cancers [6]. Conversely, for older patients with generally limited longevity and multimorbidity, the risks of perioperative morbidity and mortality are higher, and less invasive approaches may be preferable [7–9]. Alternatively, observation in the form of AS may be used for small RCMs or for patients deemed high-risk surgical candidates. However, many patients fall into a gray zone, such as a young patient with multiple comorbidities or a robust older patient. Furthermore, recent retrospective studies support guideline-based recommendations for AS for carefully selected patients with small RCMs, with a low risk of the development of metastasis and delayed intervention rates of less than 10% [10,11]. Likewise, retrospective evaluation of experience at a high-volume center concerning ablative therapies for select patients demonstrated similar rates of local recurrence and CSM to extirpation [8,12], while population-based studies demonstrate better oncologic efficacy over observation [13].

Currently, counseling for patients with cT1 RCMs relies predominantly on a subjective assessment of the risks of the disease and the benefits of procedures. However, the accuracy and precision with which urologists judge a patient's physiologic reserve and longevity are notoriously inaccurate and highly variable [14]. Thus, the objective of our study was to develop and validate models to estimate individualized treatment-specific risks of CSM, OCM, and moderate to severe complications for patients with cT1 RCMs from a large, multi-institutional cohort with heterogeneous clinicopathologic features.

2. Patients and methods

2.1. Study design, setting, and participants

Following institutional review board approval, a registry of 5847 consecutive adult patients (age $\geq$18 yr) with sporadic, unilateral, localized (cT1, cNx-0, cM0) RCMs of $\leq$10.0 cm in maximal diameter was developed from Mayo Clinic Rochester, Princess Margaret Cancer Center, Brady Urological Institute at Johns Hopkins, and University of Michigan. For the purposes of the current study, we limited our analysis to patients with cT1 masses only. Figure 1 shows the specific inclusion criteria across centers. Exclusion of patients with cT2+/x RCMs (n = 516), no follow-up (n = 27), or unspecified treatment (n = 4) yielded a final cohort of 5300 evaluable patients.

2.2. Variables, data sources, and measurements

Following diagnosis and enrollment on AS or treatment with RN, PN, or TA, patients were surveyed for disease recurrence according to institutional practices, including radiographic testing approximately every 3–6 mo for the first 2 yr and yearly thereafter. The primary outcomes of interest for this study were CSM, OCM, and moderate to severe complications within 90 d of surgery or TA (Clavien grade 3–5 complications). For patients who died, the timing and cause of death were ascertained from chart review by the treating physicians at the respective site of care.

2.3. Quantitative variables and statistical methods

Patient characteristics were stratified by primary treatment (RN, PN, TA, or AS) and compared using Kruskal-Wallis or χ^2 tests. Follow-up from the date of treatment (PN, RN, or TA) or the date of the clinic visit at

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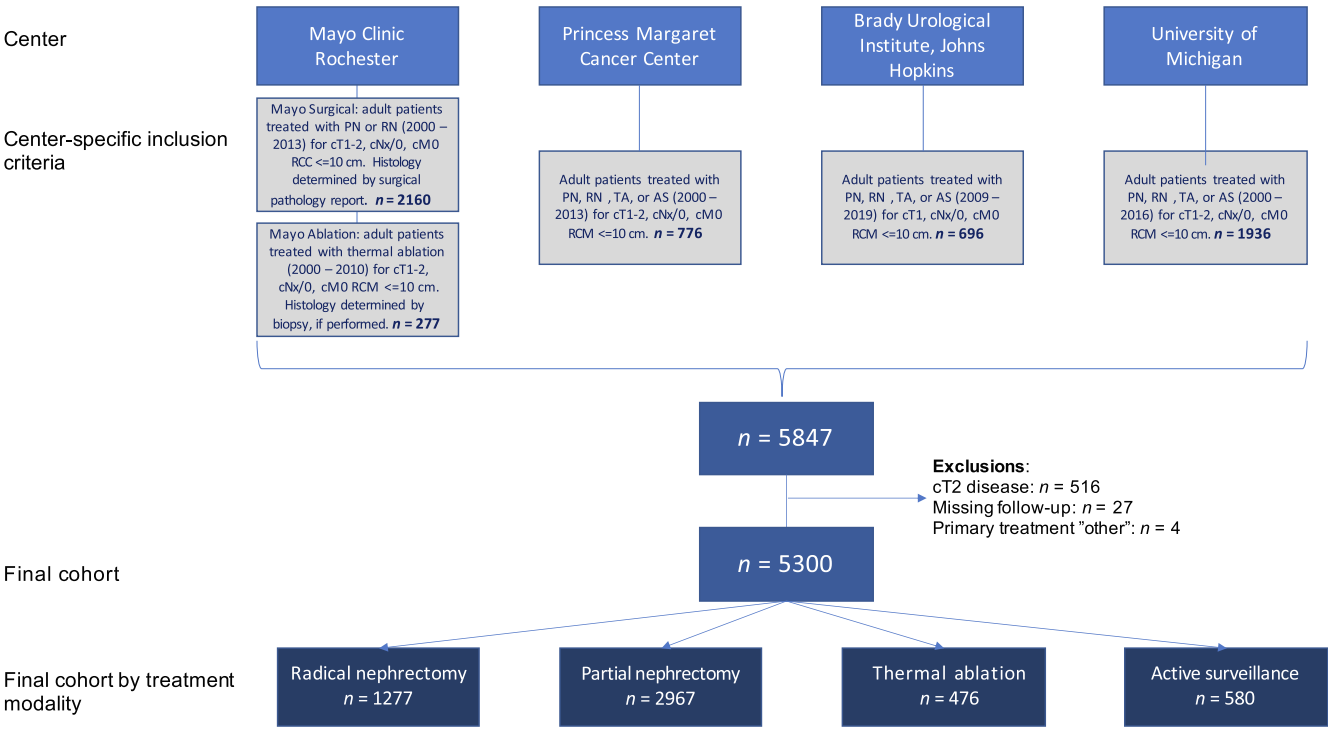

Fig. 1 – Consolidated Standards of Reporting Trials (CONSORT) diagram demonstrating patient inclusion criteria across centers, exclusion criteria, and cohort stratification by treatment. RCC = renal cell carcinoma; RCM = renal cortical mass; RN = radical nephrectomy; PN = partial nephrectomy; TA = thermal ablation; AS = active surveillance.

which AS was initiated was calculated using reverse Kaplan-Meier estimation [15]. Empirical summaries used Aalen-Johansen estimates of cumulative incidence for CSM and OCM and box plots of continuous clinicopathologic features stratified by 90-d Clavien grade 0–2 versus 3–5 complications. Outcomes of interest for this study were selected on the basis of prior empirical and comparative effectiveness work [16,17] to provide both intermediate- and long-term outcomes that could further inform decision-making, specifically for older patients and those with a high degree of comorbidity.

Variables prespecified for inclusion in the decision aid were: age (in years), sex, body mass index (BMI, categorized according to the World Health Organization thresholds), tumor diameter (in cm), Eastern Cooperative Oncology Group performance status (ECOG PS), estimated glomerular filtration rate (eGFR, categorized according to chronic kidney disease stage [18]), and Charlson comorbidity index (CCI, excluding RCM). Year of diagnosis (2000–2009 or 2010–2019) was included to account for possible period effects. Predictions for CSM and Clavien grade 3–5 complications also included the primary treatment.

Missing data for BMI (7.3%), tumor diameter (1.0%), ECOG PS (23%), eGFR (5.3%), CCI (25%), and year of diagnosis (2.7%) were imputed using fully conditional specification with predictive mean matching (tumor diameter) or polytomous regression (BMI, year of diagnosis, eGFR, ECOG PS, and CCI) accounting for race, year of diagnosis, year of treatment, BMI, eGFR, ECOG PS, CCI, American Society of Anesthesiologists score, constitutional symptoms, calcium level, hematocrit level, diabetes, smoking status, hypertension, neutrophil-to-lymphocyte ratio, pulmonary or liver disease, tumor diameter, and other malignancies. Fitted imputation models were used to generate ten data sets, and risk prediction models adjusted for the decision-aid variables selected were fitted to each data set. Estimates from the risk prediction models were combined across data sets according to Rubin's rules after complementary log-log (for CSM and OCM) or logarithmic (for Clavien grade 3–5 complications) transformations [19].

To evaluate the performance of the risk prediction model, ten bootstrap samples were drawn from the original data set. The imputation model and prediction model fitting and procedure for combining across estimates were repeated for each bootstrap sample. Discrimination and calibration of the final risk predictions for 90-d complications and 5-yr CSM and OCM from each bootstrap sample were then evaluated using the original data set [20]. Discrimination between patients with and without events was assessed using the median and interquartile range (IQR) of the concordance index (C-index) across ten bootstrap samples and visualized using receiver operating characteristic (ROC) curves. Calibration of absolute risks was assessed using the median and 95% quantile intervals of the empirical proportions of events corresponding to a ten-group partition of the range of predicted probabilities for each outcome across ten bootstrap samples with ten imputed data sets for each sample.

Following this bootstrap validation [20,21], final models based on the full data set ($n = 5300$) were used to predict outcomes for each treatment over an exhaustive grid of possible clinical and tumor features. An online calculator was developed to provide direct access to individualized predictions. Decision curve analyses for 5-yr CSM and OCM and 90-d severe complications were performed.

Statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided and $p < 0.05$ was considered statistically significant. Results from the study are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement on guidelines for reporting observational studies [22].

3. Results

3.1. Participants and descriptive data

Of the 5300 patients included in the study, 1277 (24%) were treated with RN, 2967 (56%) underwent PN, 476 (9.0%) were

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treated with TA, and 580 (11%) were managed with AS. Clinical and demographic features of the cohort are presented in Table 1. Among the surgical patients, 802/1277 (63%) of those undergoing RN and 1358/2967 (46%) undergoing PN were treated with a minimally invasive approach. Lymphadenectomy was performed in 147/1277 (12%) RN patients and 30/2967 (1.0%) PN patients. Among 476 patients treated with TA, 262 (55%) underwent percutaneous radiofrequency ablation (RFA), 153 (32%) underwent percutaneous cryoablation, 57 (12%) received laparoscopic cryoablation, three (0.63%) underwent laparoscopic RFA, and one (0.21%) was treated with open cryoablation.

3.2. Outcome data

Over median follow-up of 5.2 yr (IQR 2.5–8.7), 117 patients died from RCC and 607 died from other causes. The 5-yr and 10-yr CSM was 2.0% and 3.7%, and 5-yr and 10-yr OCM was 9.3% and 21%, respectively. A total of 198/4720 (4.2%) patients experienced 90-d Clavien 3–5 complications, including 34/1277 (2.7%) in the RN group, 150/2967 (5.1%) in the PN group, and 14/476 (2.9%) in the TA group. Death within 90 d was observed for 2/1277 (0.16%) patients treated with RN and two out of 2967 (0.067%) patients treated with PN.

3.3. Main results

Patients treated with nephrectomy had a higher probability of CSM and a lower probability of OCM compared to those treated with TA or AS (Fig. 2). Unsurprisingly, OCM was higher for the groups with ECOG PS 2–4 or CCI 1–12 (Supplementary Figs. 1 and 2). Supplementary Figure 3 demonstrates variation in Clavien 3–5 complications across definitive treatments (RN, PN, and TA). Of note, larger tumors were associated with complications after PN ($p < 0.001$) while lower pretreatment eGFR was associated with complications after RN ($p < 0.001$) after Bonferroni adjustment for the 12 comparisons.

Table 1 – Clinical and demographic features of the study cohort

	RN	PN	TA	AS	*p* value [a]
n	1277	2967	476	580	
Median age (*N* = 5300), yr (IQR)	63 (54–72)	59 (50–67)	71 (63–76)	71 (64–79)	<0.001
Male (*N* = 5300), *n* (%)	796 (62)	1916 (64)	302 (63)	349 (60)	0.17
Race (*N* = 4865), *n* (%)					<0.001
White	1003 (89)	2516 (91)	406 (90)	413 (81)	
Black/African American	53 (4.7)	119 (4.3)	16 (3.5)	77 (15.0)	
Asian	29 (2.6)	60 (2.2)	5 (1.1)	14 (2.7)	
Other	38 (3.4)	84 (3.0)	24 (5.3)	8 (1.6)	
Site (*N* = 5300), *n* (%)					<0.001
Mayo Clinic	528 (41)	1389 (47)	271 (57)	0 (0.0)	
Toronto	228 (18)	253 (8.5)	60 (13)	153 (26)	
Johns Hopkins	43 (3.4)	275 (9.3)	28 (5.9)	344 (59)	
Michigan	478 (37)	1050 (35)	117 (25)	83 (14)	
Year of diagnosis 2010–2019 (*N* = 5155), *n* (%)	376 (30)	1291 (45)	101 (23)	419 (72)	<0.001
Median calcium (*N* = 2859), mg/dl (IQR)	9.5 (9.2–9.8)	9.6 (9.3–9.9)	9.6 (9.2–9.9)	9.6 (9.1–9.9)	0.008
Median hemoglobin (*N* = 4134), g/dl (IQR)	14 (13–15)	14 (13.1–15.1)	14 (12–15)	13 (12–15)	<0.001
Median albumin (*N* = 1856), g/dl (IQR)	4.2 (3.9–4.4)	4.3 (4.1–4.5)	4.2 (3.8–4.4)	4.2 (3.9–4.5)	<0.001
Median eGFR (*N* = 5020), ml/min/1.73 m^2 (IQR)	70 (53–85)	77 (62–92)	63 (48–81)	68 (50–83)	<0.001
Median BMI (*N* = 4909), kg/m^2 (IQR)	29 (26–34)	29 (26–34)	30 (26–34)	28.3 (25–32)	<0.001
BMI category (*N* = 4909), *n* (%)					0.001
11.25–24.9 kg/m^2	260 (22)	510 (18)	75 (19)	111 (24)	
25.0–29.9 kg/m^2	406 (34)	1002 (35)	131 (32)	184 (40)	
30.0–34.9 kg/m^2	325 (27)	737 (26)	112 (28)	102 (22)	
35.0–39.9 kg/m^2	119 (9.9)	341 (12)	42 (10)	39 (8.4)	
40.0–74.9 kg/m^2	93 (7.7)	245 (8.6)	45 (11)	30 (6.4)	
Median tumor size (*N* = 5248), cm (IQR)	4.6 (3.3–6.0)	3.0 (2.1–4.0)	2.5 (2.0–3.2)	1.9 (1.4–2.7)	<0.001
Constitutional symptoms (*N* = 3436), *n* (%)	97 (12)	134 (7.1)	77 (22)	21 (5.3)	<0.001
Weight loss (*N* = 3425), *n* (%)	34 (4.3)	50 (2.6)	15 (4.2)	12 (3.0)	0.097
Night sweats (*N* = 2878), *n* (%)	4 (0.5)	9 (0.5)	2 (0.6)	3 (2.0)	0.2
Hematuria (*N* = 3562), *n* (%)	137 (17)	154 (8.1)	10 (2.8)	47 (9.5)	<0.001
Flank pain (*N* = 3567), *n* (%)	151 (19)	267 (14)	38 (11)	27 (5.4)	<0.001
Flank mass (*N* = 3567), *n* (%)	6 (0.8)	6 (0.3)	1 (0.3)	0 (0.0)	0.15
Jaundice (*N* = 2879), *n* (%)	5 (0.7)	3 (0.2)	0 (0.0)	0 (0.0)	0.12
Lower-extremity edema (*N* = 2879), *n* (%)	49 (6.5)	118 (7.2)	18 (5.4)	1 (0.7)	0.01
Thromboembolic events (*N* = 3552), *n* (%)	44 (5.5)	83 (4.3)	9 (2.5)	20 (4.1)	0.13
ECOG PS 2–4 (N = 4106), *n* (%)	47 (5.4)	46 (2.0)	52 (13)	25 (5.2)	<0.001
ASA score 3–4 (*N* = 4208), *n* (%)	635 (55)	1181 (43)	209 (70)	18 (70)	<0.001
CCI (*N* = 3949), *n* (%)					<0.001
1–2	369 (41)	773 (36)	141 (39)	195 (38)	
3–12	215 (24)	368 (17)	112 (31)	123 (24)	
Smoking status (*N* = 4486), *n* (%)					<0.001
Never smoked	452 (45)	1154 (46)	186 (44)	310 (56)	
Current smoker	152 (15)	407 (16)	45 (11)	51 (9.2)	
Former smoker	396 (40)	948 (38)	192 (45)	190 (34)	
Unknown	0 (0.0)	1 (0.0)	0 (0.0)	2 (0.4)	

RN = radical nephrectomy; PN = partial nephrectomy; TA = thermal ablation; IQR = interquartile range; eGFR = estimated glomerular filtration rate; BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; AS = active surveillance; ASA = American Anesthesiologists Association; CCI = Charlson comorbidity index.

[a] Continuous variables were compared using a Kruskal-Wallis test and categorical variables were compared using a χ^2 test.

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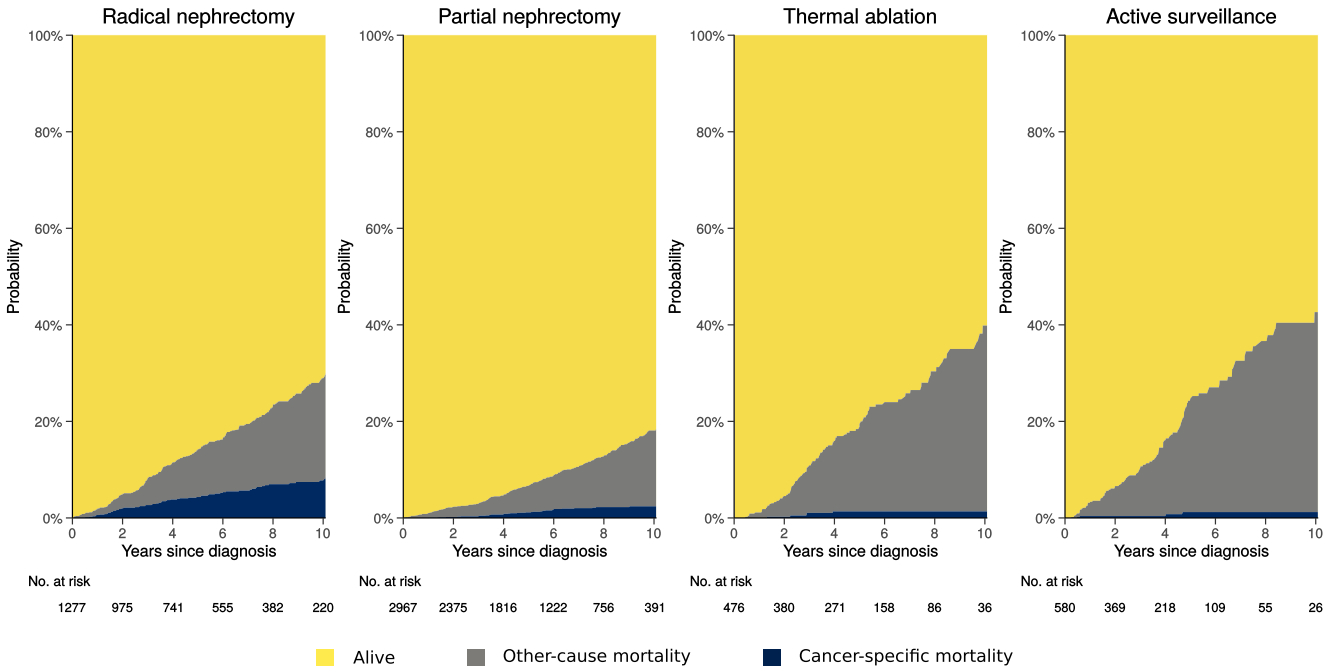

Fig. 2 – Cumulative incidence of cancer-specific mortality and other-cause mortality by treatment.

The fitted risk models (Supplementary Tables 1–3) predicted that larger tumor diameter and higher CCI were associated with higher risk of CSM and odds of Clavien 3–5 complications. The risk of CSM was not significantly different across treatments or calendar periods. The odds of Clavien 3–5 complications were higher for patients treated with PN ($p < 0.001$) compared to RN. Male sex, higher ECOG PS, and higher CCI were associated with higher risk of OCM.

ROC curves demonstrated acceptable discrimination for 5-yr CSM (median concordance index/area under the curve [AUC] 0.80, IQR 0.79–0.81) and OCM (AUC 0.77, IQR 0.77–0.77) and slightly lower discrimination for 90-d complications (AUC 0.64, IQR 0.64–0.65). Calibration plots for ten bootstrap samples indicate moderate upward bias in predicted risks of 5-yr CSM and OCM among patients in the highest risk groups (Supplementary Fig. 4A). Decision curve analysis indicated that the risk calculator outperforms all-or-nothing predictions for these outcomes, although differences are modest when these outcomes are unlikely, as they are for 5-yr CSM and 90-d complications (Supplementary Fig. 4B). If patients would only consider definitive treatment (RN, PN, or TA) if their risk of 5-yr CSM were high (>10%), then the risk calculator is unlikely to be more useful than a simple prediction as this outcome is very rare. A similar conclusion applies if their threshold for considering different definitive treatments requires the risk of 90-d complications to be high (>10%). However, if the thresholds for action based on these outcomes are lower, if the risk of 5-yr OCM is determinative and their threshold for action is nontrivial (>2%), or if more than one outcome is relevant to decision-making around treatment [23], then the risk calculator promises greater clinical utility than simple all-or-nothing predictions.

Results from the final risk prediction models are available via an online calculator (https://small-renal-mass-risk-calculator.fredhutch.org), where a user can input individual patient characteristics to obtain personalized treatment-specific risk predictions in a clinical setting. Figure 3 shows exemplar outputs for a patient with a 4.5-cm RCM and varying clinical parameters.

4. Discussion

Patients with cT1 RCMs often present a treatment dilemma given that guideline-based care options may include AS, TA, and surgical extirpation via either PN or RN [1,2]. While decision-making may be straightforward for patients in otherwise good health, for patients with competing comorbidities or significant functional deficits, the calculus is complex.

In this manuscript we present risk prediction models derived from 5300 patients with cT1 RCMs treated with AS, TA, PN, or RN that estimate personalized, treatment-specific 5-yr and 10-yr risks of CSM and OCM as well as the 90-d risk of moderate to severe complications. The models permit patients and clinicians to evaluate estimates of these short- and long-term outcomes across treatments. Model covariates were selected on the basis of medical and empirical relevance, and traditional statistical models were used to facilitate interpretation and draw inference. The predictions incorporate granular patient-specific data that are easily obtained at initial consultation, including performance status, comorbidity burden, BMI, and baseline kidney function.

Notably, especially with smaller masses, patients with localized, node-negative RCMs have low 5-yr CSM overall. However, OCM increases significantly with increasing burden of comorbidities and decreasing performance status. Complication rates also increase with ECOG PS and tumor

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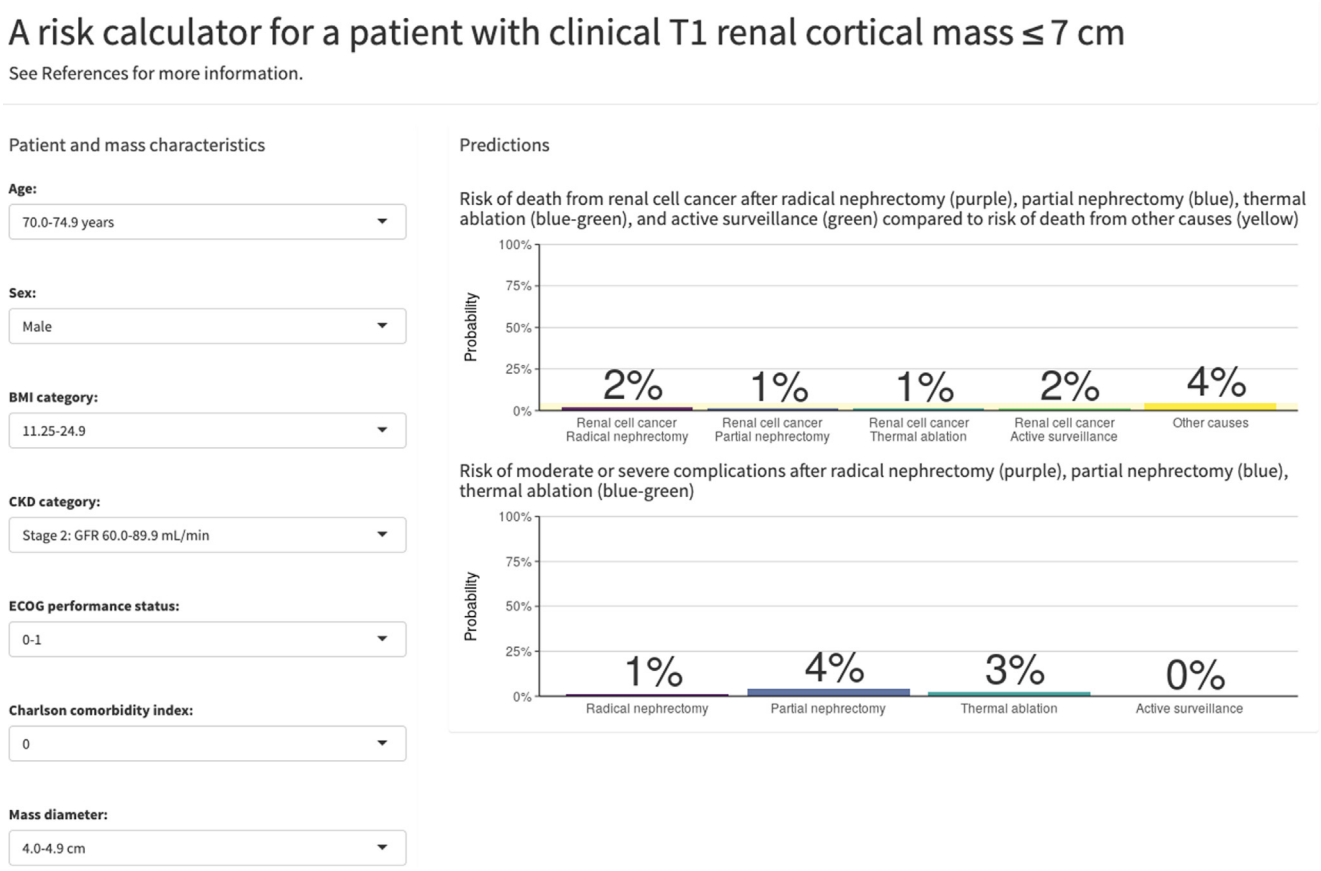

Fig. 3 – Example of competing-risks predictions for 5-yr cancer-specific mortality by treatment, other-cause mortality, and 90-d complications for (A) a 74-yr-old male with a 4.5-cm RCM, BMI of 24 kg/m^2, eGFR of 60 ml/min, ECOG PS of 0, and CCI of 1 compared to (B) a 74-yr-old male with a 4.5-cm RCM, BMI of 32 kg/m^2, eGFR of 50 ml/min, ECOG PS of 3, and CCI of 3. BMI = body mass index; CCI = Charlson comorbidity index; ECOG PS = Eastern Cooperative Oncology Group performance status; eGFR = estimated glomerular filtration rate; RCM = renal cortical mass.

size, specifically for nephron-sparing treatments. Having both short- and long-term estimates offers significant potential benefits for patients with multiple medical risks in terms of providing quantitative predictions underlying the critical trade-offs across treatments. For example, in a patient with high risk of 5-yr OCM, the relevance of risk of major complications within 90 d may be weighed more heavily given the potential impact on short-term quality of life. While this calculus is commonly introduced in shared decision-making, quantification of these trade-offs generally relies on qualitative gestalt estimates made by the treating surgeon that are based on clinical experience. However, physician estimates of a patient's life expectancy following an initial cancer diagnosis are frequently inaccurate, underscoring the need for validated estimates to quantify these trade-offs [14,24,25].

Multiple authors have developed nomograms to improve estimates of competing risks. Hollingsworth and colleagues [26] proposed a model including age at diagnosis, race, marital status, and type of surgery, and concluded that patients with small renal masses benefit the least from surgery with respect to risk of CSM. However, the model did not incorporate comorbidity. Kutikov and colleagues [17] developed a competing-risks nomogram in a Surveillance, Epidemiology and End Results (SEER)-based cohort of more than 30 000 patients with surgically resected localized renal cell carcinomas. However, this model similarly did not account for comorbidity, and would not apply to patients who did not undergo surgery. In a subsequent iteration, the authors presented a comorbidity-based model of competing risks of death that generated estimates of 5-yr CSM, death from other malignancies, and noncancer death based on age, sex, race, tumor size, and CCI; however, the calculator was limited to patients older than 66 yr treated with surgery [16]. Furthermore, granular data, such as performance status and BMI, were not accounted for.

Importantly, prior studies were limited to patients who underwent surgery. They did not include patients managed expectantly or on AS protocols, or patients treated with TA. Furthermore, these studies were also limited to patients with confirmed renal cell carcinoma on final pathology, and thus may have limited generalizability to patients with indolent histology or benign masses. In the current study, patients with a cT1 RCM were included irrespective of pathology. While percutaneous biopsy is an option to discern histology in this scenario [1], it remains underutilized in contemporary practice [27]. To illustrate, in the current cohort, biopsy was only performed in 24% of patients and was not included in the predictive models presented. In general, treatment decisions are commonly made according to imaging alone; however, as current guidelines would advocate, biopsies should be performed in all patients con-

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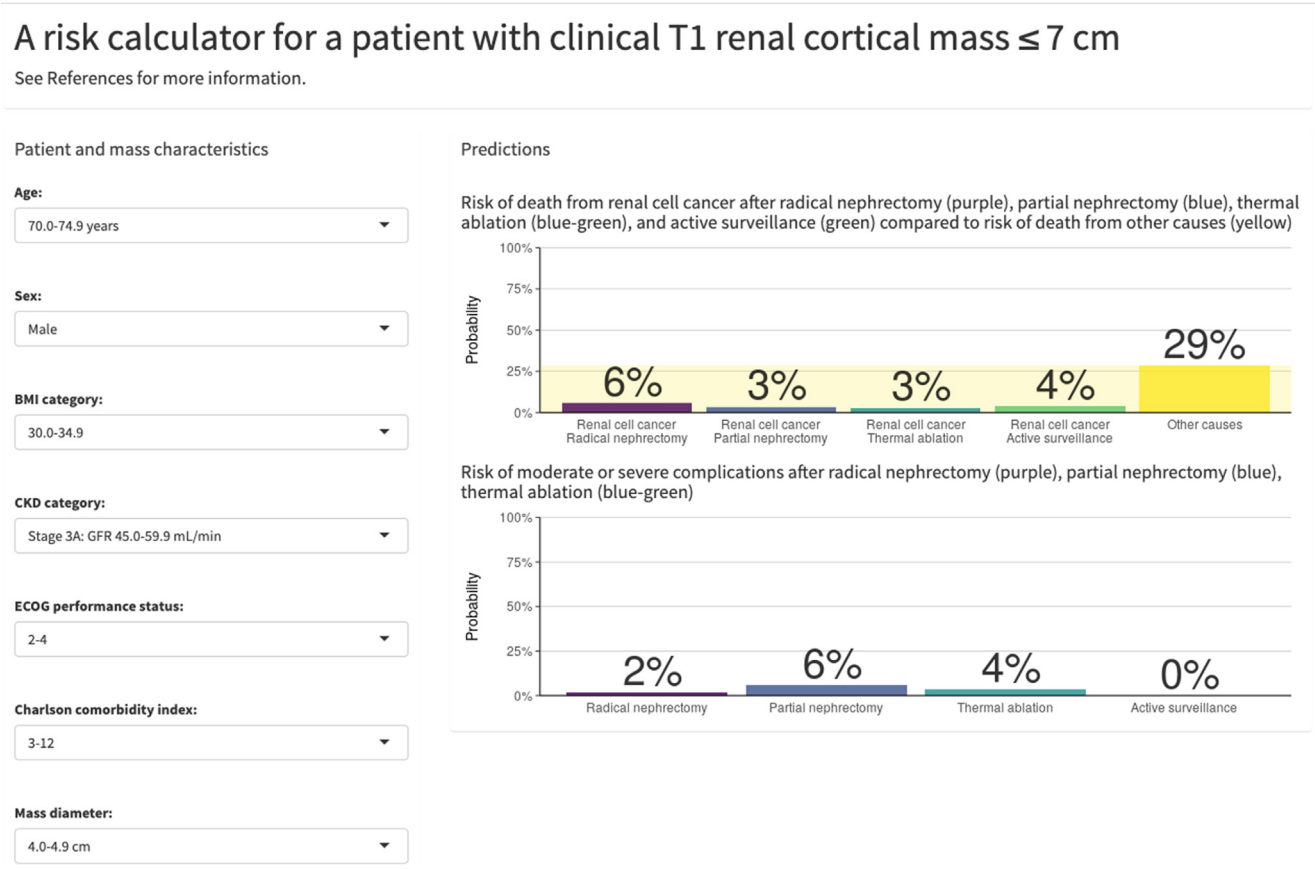

Fig. 3 (*continued*)

sidering TA and should be considered in patients for whom the histologic diagnosis would influence decision-making [1]. In addition, few prior studies have included outcomes among patients who did not undergo active intervention, and we are not aware of any studies to date that included performance status. Finally, we are not aware of any nomograms that incorporated individualized quantification of the risks of morbidity or mortality related to the treatment strategies themselves.

Prior studies that quantified competing risks for patients with small and localized renal cell carcinoma relied largely on the SEER database and other administrative data sets, demonstrating the complex interplay of age and comorbidity [28–32]. In addition, the current study incorporates several patient-specific variables not included in previously published models, including BMI and baseline kidney function.

Regarding BMI, a recent meta-analysis of 10 512 patients with renal cell carcinoma demonstrated that increasing BMI was paradoxically associated with decreasing CSM but increasing OCM [33]. BMI is also variably associated with complications after RN and PN [34]. Schmit and colleagues [35] reported similar complication rates following percutaneous cryoablation of small renal masses among 367 patients, of whom 161 were obese and 39 were morbidly obese. Consistent with these findings, we did not observe associations between increasing BMI and odds of 90-d Clavien grade 3–5 complications across treatments.

Baseline renal function represents a key clinical parameter assessed during treatment selection for cT1 RCMs given the potential implications for subsequent renal function decline if a patient elects to undergo RN versus a nephron-sparing treatment (PN, TA, or AS). Nephron-sparing approaches are preferred when possible to avoid the risks of severe decline in renal function, eventual end-stage renal dysfunction, and subsequent hypertension, which have significant implications for long-term overall survival [36–38] and health-related quality of life [39]. However, a randomized trial and other observational studies have failed to demonstrate an association between overall survival and the risk of chronic kidney disease after RN [37,40]. For patients with complex or larger masses or with greater surgical risks, the higher risks of prolonged anesthesia and perioperative complications with nephron-sparing approaches must also be weighed [41]. The current risk calculator incorporates baseline renal function in its estimation of competing risks, which may complement the output of previously published tools that predict post-treatment renal function on the basis of preoperative patient-based factors [42], imaging assessments of tumor volume and renal scintigraphy [43], and tumor complexity [44].

This study has several potential limitations. First, selection bias and variation in practice patterns across the treatment sites and over time may have influenced the results of this retrospective study: as expected, there was substantial

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heterogeneity in baseline characteristics across the treatment cohorts, and the estimates generated by the final models are subject to unmeasured confounding. We did evaluate heterogeneity across centers and found that associations with age, sex, and tumor diameter were generally robust. There was mixed evidence that associations with ECOG PS varied across centers, which we attribute to differing baseline risks. In addition, the study cohort may be influenced by variations in practice patterns by surgeon volume and by center; however, variation by surgeon volume was not assessed as surgeon identifiers were not available in the data set. A sensitivity analysis excluding all patients from the center with the majority of missing ECOG PS and CCI data (Michigan) materially altered the predicted risks, although differences across ECOG PS and CCI strata were limited relative to the overall differences (data not shown). Consequently, we retained this center in the main analysis for data efficiency to reflect greater variation across centers and to improve the generalizability of our results.

Assessments of practice patterns suggest that RN was more commonly used for cT1a and cT1b renal masses than PN early on, with increasing recent preference for nephron-sparing approaches. In addition, TA and AS were rarely utilized at the beginning of the study timeframe but have gained increasing acceptance in contemporary practice. We found that CSM after TA was significantly lower in later years, possibly owing to a learning curve. To reflect contemporary patients, our online calculator uses predictions of baseline risk of CSM and of complications relevant to the most recent decade of experience. Owing to data limitations, treatment-specific period effects could not be reliably estimated. Furthermore, some centers contributed data for specific treatment groups only; for example, the Mayo Clinic did not provide data for patients enrolled on AS. Therefore, there are fewer representative patients in the current cohort managed with AS, which may further limit the generalizability of these risk predictions. Importantly, the multicenter data set for the cohort included only data for the initial treatment strategy and not for subsequent treatments, such as the number of patients who transitioned from AS to definitive treatment or who underwent initial PN or TA and subsequently developed recurrence and received either RN or required systemic therapy. In addition, there were few patients (n = 30/5300, 0.57%) in the data set meeting the BMI criterion for "underweight" (<18.5 kg/m^2). Given the small number of patients in this category and the lack of stability of estimates for this group, these patients were combined with patients with normal weight, potentially limiting the generalizability of our estimates for underweight patients. We also acknowledge that the prediction model for complications in this data set demonstrated lower discrimination (C index 0.64) compared to the models for CSM and OCM, which may reflect the relatively low event rate for complications in the data set. Thus, patient counseling regarding the individualized risk of complications after PN or RN might benefit from the inclusion of other robust, validated risk calculators such as the American College of Surgeons NSQIP risk calculator in the risk assessment [45], although this calculator does not predict the risk of adverse outcomes following TA. Similarly, the decision curve analysis indicates limited advantages over all-or-nothing predictions for 5-yr CSM and 90-d Clavien complications. However, this evaluation does not account for how a patient might prioritize or weight personalized estimates of both short- and long-term outcomes during treatment decision-making.

Finally, while this study includes carefully collected preoperative personalized covariates, it does not include relevant factors that could influence outcomes, including patient frailty [46–48] and nutritional status [49], or specific features related to tumor anatomy, such as the RENAL nephrometry score [50–52], nor does it include all potential outcomes that may be relevant to a specific patient, including discharge disposition following treatment, return versus maintenance of physical function, preservation of renal function, future burden of surveillance visits and imaging assessments, impact on mental health outcomes (eg, anxiety, decisional conflict) [23], or intermediate oncologic outcomes such as recurrence-free survival. To underscore this point, a recent collaborative review by Chandrasekar et al [23] highlights the complexity and variability in the potential salient outcomes for individuals with localized renal masses who are considering different treatment options. In addition, while we included CCI as a surrogate for comorbidity burden, there is increasing awareness that more granular assessments of comorbidity are available and may be more relevant when quantifying multimorbidity and its relevance in a surgical population [53,54]. As detailed by the authors, no single tool or statistical model can replace a carefully considered counseling visit based around shared-decision-making with an experienced physician. However, the estimates generated by the models presented here may further inform these discussions, permitting patients to better understand their personalized risk predictions of periprocedural complications and long-term survival outcomes associated with each treatment. Because the risk predictions are only for an incomplete set of outcomes relevant to shared decision-making, we did not evaluate their clinical utility using established methods such as decision curve analysis [55]. It is also of note that outcomes were assessed by the treating physicians at each center via retrospective review of electronic health records rather than centralized review of certified death records. By assessing performance using bootstrap samples, the potential for overfitting or unsupported optimism is controlled, and data from all patients can be used in the final fitted models. However, external validation using data for patients treated at other institutions is necessary to establish broader generalizability of the predicted risks.

5. Conclusions

In summary, we present novel clinical risk prediction models of mortality and 90-d periprocedural moderate to severe complications for patients with a localized RCM $\leq$7 cm, accounting for tumor size, patient age, sex, BMI, ECOG PS, and CCI across standard treatments. This tool generates personalized, treatment-specific risk estimates of short- and long-term outcomes, providing individualized projections regarding the potential trade-offs for each treatment option

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for a patient and their providers to inform shared decision-making regarding management of a cT1 RCM.

Author contributions: Sarah P. Psutka 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: Psutka, Gulati, Jewett, Shah, Leibovich.
Acquisition of data: Psutka, Lohse, Thompson, Atwell, Schmit, Fadaak, Finelli, Legere, Morgan, Pierorazio, Allaf, Lohse, Thompson, Boorjian, Costello, Leibovich.
Analysis and interpretation of data: Psutka, Gulati, Herrin, Lohse.
Drafting of the manuscript: Psutka, Gulati.
Critical revision of the manuscript for important intellectual content: Jewett, Fadaak, Finelli, Morgan, Pierorazio, Allaf, Lohse, Thompson, Boorjian, Atwell, Schmit, Costello, Shah, Leibovich.
Statistical analysis: Psutka, Gulati, Herrin, Lohse.
Obtaining funding: None.
Administrative, technical, or material support: Jewett, Morgan, Pierorazio, Allaf, Thompson, Shah, Leibovich.
Supervision: Shah, Leibovich, Jewett.
Other: None.

Financial disclosures: Sarah P. Psutka 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: None.

Acknowledgments: Roman Gulati is supported by National Institutes of Health grant R50 CA221836.

Peer Review Summary

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2021.11.002.

References

[1] Campbell S, Uzzo RG, Allaf ME, et al. Renal mass and localized renal cancer: AUA guideline. J Urol 2017;198:520–9.
[2] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: kidney cancer version 2.2021. Plymouth Meeting, PA: NCCN; 2021.
[3] Ljungberg B, Albiges L, Bedke J, et al. EAU guidelines: renal cell carcinoma. Arnhem, The Netherlands: European Association of Urology; 2021.
[4] National Health Commission of the People's Republic of China. Chinese guidelines for diagnosis and treatment of renal cell carcinoma 2018 (English version). Chin J Cancer Res 2018;2019:29–48.
[5] Shah PH, Alom MA, Leibovich BC, et al. The temporal association of robotic surgical diffusion with overtreatment of the small renal mass. J Urol 2018;200:981–8.
[6] Kunkle DA, Haas NB, Uzzo RG. Adjuvant therapy for high-risk renal cell carcinoma patients. Curr Urol Rep 2007;8:19–30.
[7] An JY, Ball MW, Gorin MA, et al. Partial vs radical nephrectomy for T1–T2 renal masses in the elderly: comparison of complications, renal function, and oncologic outcomes. Urology 2017;100:151–7.
[8] Pierorazio PM, Johnson MH, Patel HD, et al. Management of renal masses and localized renal cancer: systematic review and meta-analysis. J Urol 2016;196:989–99.
[9] Thompson RH, Atwell T, Schmit G, et al. Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. Eur Urol 2015;67:252–9.
[10] Pierorazio PM, Johnson MH, Ball MW, et al. Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. Eur Urol 2015;68:408–15.
[11] Mir MC, Capitanio U, Bertolo R, et al. Role of active surveillance for localized small renal masses. Eur Urol Oncol 2018;1:177–87.
[12] Andrews JR, Atwell T, Schmit G, et al. Oncologic outcomes following partial nephrectomy and percutaneous ablation for cT1 renal masses. Eur Urol 2019;76:244–51.
[13] Larcher A, Trudeau V, Sun M, et al. Population-based assessment of cancer-specific mortality after local tumour ablation or observation for kidney cancer: a competing risks analysis. BJU Int 2016;118:541–6.
[14] Wilson JR, Clarke MG, Ewings P, Graham JD, MacDonagh R. The assessment of patient life-expectancy: how accurate are urologists and oncologists? BJU Int 2005;95:794–8.
[15] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343–6.
[16] Kutikov A, Egleston BL, Canter D, Smaldone MC, Wong YN, Uzzo RG. Competing risks of death in patients with localized renal cell carcinoma: a comorbidity based model. J Urol 2012;188:2077–83.
[17] Kutikov A, Egleston BL, Wong YN, Uzzo RG. Evaluating overall survival and competing risks of death in patients with localized renal cell carcinoma using a comprehensive nomogram. J Clin Oncol 2010;28:311–7.
[18] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2012;2013:1–150.
[19] Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol 2009;9:57.
[20] Steyerberg EW, Harrell Jr FE, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001;54:774–81.
[21] Steyerberg EW, Harrell Jr FE. Prediction models need appropriate internal, internal-external, and external validation. J Clin Epidemiol 2016;69:245–7.
[22] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.
[23] Chandrasekar T, Boorjian SA, Capitanio U, Gershman B, Mir MC, Kutikov A. Collaborative review: factors influencing treatment decisions for patients with a localized solid renal mass. Eur Urol 2021;80:575–88.
[24] Christakis NA, Lamont EB. Extent and determinants of error in physicians' prognoses in terminally ill patients: prospective cohort study. West J Med 2000;172:310–3.
[25] Lamont EB, Christakis NA. Complexities in prognostication in advanced cancer: "to help them live their lives the way they want to". JAMA 2003;290:98–104.
[26] Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Five-year survival after surgical treatment for kidney cancer: a population-based competing risk analysis. Cancer 2007;109:1763–8.
[27] Shahait M, Jackman S, Landman J, et al. Utilization and operative influence of renal mass biopsy in the small renal mass: analysis from the Clinical Research Office of the Endourological Society Small Renal Mass registry. J Endourol 2020;34:99–106.
[28] Bianchi M, Gandaglia G, Trinh QD, et al. A population-based competing-risks analysis of survival after nephrectomy for renal cell carcinoma. Urol Oncol 2014;32:e1–7.
[29] Sun M, Abdollah F, Bianchi M, et al. A stage-for-stage and grade-for-grade analysis of cancer-specific mortality rates in renal cell carcinoma according to age: a competing-risks regression analysis. Eur Urol 2011;60:1152–9.
[30] Sun M, Bianchi M, Trinh QD, et al. Comparison of partial vs radical nephrectomy with regard to other-cause mortality in T1 renal cell

carcinoma among patients aged ≥75 years with multiple comorbidities. BJU Int 2013;111:67–73.
[31] Patel HD, Kates M, Pierorazio PM, et al. Comorbidities and causes of death in the management of localized T1a kidney cancer. Int J Urol 2014;21:1086–92.
[32] Patel HD, Kates M, Pierorazio PM, et al. Survival after diagnosis of localized T1a kidney cancer: current population-based practice of surgery and nonsurgical management. Urology 2014;83:126–32.
[33] Bagheri M, Speakman JR, Shemirani F, Djafarian K. Renal cell carcinoma survival and body mass index: a dose-response meta-analysis reveals another potential paradox within a paradox. Int J Obes 2016;40:1817–22.
[34] Arora K, Hanson K, Habermann EB, Tollefson MK, Psutka SP. Nutritional predictors of perioperative complications and mortality following nephrectomy for renal malignancies: a population-based analysis. Kidney Cancer 2018;2:147–74.
[35] Schmit GD, Thompson RH, Boorjian SA, et al. Percutaneous renal cryoablation in obese and morbidly obese patients. Urology 2013;82:636–41.
[36] Shah PH, Leibovich BC, Van Houten H, et al. Association of partial versus radical nephrectomy with subsequent hypertension risk following renal tumor resection. J Urol 2019;202:69–75.
[37] Gershman B, Thompson RH, Boorjian SA, et al. Radical versus partial nephrectomy for cT1 renal cell carcinoma. Eur Urol 2018;74: 825–32.
[38] Capitanio U, Larcher A, Cianflone F, et al. Hypertension and cardiovascular morbidity following surgery for kidney cancer. Eur Urol Oncol 2020;3:209–15.
[39] Lesage K, Joniau S, Fransis K, Van Poppel H. Comparison between open partial and radical nephrectomy for renal tumours: perioperative outcome and health-related quality of life. Eur Urol 2007;51:614–20.
[40] Van Poppel H, Da Pozzo L, Albrecht W, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol 2011;59: 543–52.
[41] Kim SP, Campbell SC, Gill I, et al. Collaborative review of risk benefit trade-offs between partial and radical nephrectomy in the management of anatomically complex renal masses. Eur Urol 2017;72:64–75.
[42] Bhindi B, Lohse CM, Schulte PJ, et al. Predicting renal function outcomes after partial and radical nephrectomy. Eur Urol 2019;75: 766–72.
[43] Mitsui Y, Sadahira T, Araki M, et al. The 3-D volumetric measurement including resected specimen for predicting renal function after robot-assisted partial nephrectomy. Urology 2019;125:104–10.
[44] Bertolo R, Garisto J, Li J, Dagenais J, Kaouk J. Development and internal validation of a nomogram for predicting renal function after partial nephrectomy. Eur Urol Oncol 2019;2:106–9.
[45] Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. J Am Coll Surg 2013;217:e1–3.
[46] Revenig LM, Canter DJ, Taylor MD, et al. Too frail for surgery? Initial results of a large multidisciplinary prospective study examining preoperative variables predictive of poor surgical outcomes. J Am Coll Surg 2013;217.
[47] Joseph B, Pandit V, Sadoun M, et al. Frailty in surgery. J Trauma Acute Care Surg 2014;76:1151–6.
[48] Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin 2017;67:362–77.
[49] Morgan TM, Tang D, Stratton KL, et al. Preoperative nutritional status is an important predictor of survival in patients undergoing surgery for renal cell carcinoma. Eur Urol 2011;59:923–8.
[50] Camacho JC, Kokabi N, Xing M, et al. R.E.N.A.L. (radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines) nephrometry score predicts early tumor recurrence and complications after percutaneous ablative therapies for renal cell carcinoma: a 5-year experience. J Vasc Interv Radiol 2015;26: 686–93.
[51] Dahlkamp L, Haeuser L, Winnekendonk G, et al. Interdisciplinary comparison of PADUA and R.E.N.A.L. scoring systems for prediction of conversion to nephrectomy in patients with renal mass scheduled for nephron sparing surgery. J Urol 2019;202:890–8.
[52] Schiavina R, Novara G, Borghesi M, et al. PADUA and R.E.N.A.L. nephrometry scores correlate with perioperative outcomes of robot-assisted partial nephrectomy: analysis of the Vattikuti Global Quality Initiative in Robotic Urologic Surgery (GQI-RUS) database. BJU Int 2017;119:456–63.
[53] Psutka SP, Barocas DA, Catto JWF, et al. Staging the host: personalizing risk assessment for radical cystectomy patients. Eur Urol Oncol 2018;1:292–304.
[54] Garg T, Young AJ, Kost KA, et al. Burden of multiple chronic conditions among patients with urological cancer. J Urol 2018;199: 543–50.
[55] Elkin EB, Vickers AJ, Kattan MW. Primer: using decision analysis to improve clinical decision making in urology. Nat Clin Pract Urol 2006;3:439–48.

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