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Predicting Disease Recurrence, Early Progression, and Overall Survival Following Surgical Resection for High-risk Localized and Locally Advanced Renal Cell Carcinoma

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Andres F. Correa 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.

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Abstract

Background: Risk stratification for localized renal cell carcinoma (RCC) relies heavily on retrospective models, limiting their generalizability to contemporary cohorts.

Objective: To introduce a contemporary RCC prognostic model, developed using prospective, highly annotated data from a phase III adjuvant trial.

Design, setting, and participants: The model utilizes outcome data from the ECOG-ACRIN 2805 (ASSURE) RCC trial.

Outcome measurements and statistical analysis: The primary outcome for the model is disease-free survival (DFS), with overall survival (OS) and early disease progression (EDP) as secondary outcomes. Model performance was assessed using discrimination and calibration tests.

Results and limitations: A total of 1735 patients were included in the analysis, with 887 DFS events occurring over a median follow-up of 9.6 yr. Five common tumor variables (histology, size, grade, tumor necrosis, and nodal involvement) were included in each model. Tumor histology was the single most powerful predictor for each model outcome. The C-statistics at 1 yr were 78.4% and 81.9% for DFS and OS, respectively. Degradation of the DFS, DFS validation set, and OS model's discriminatory ability was seen over time, with a global c-index of 68.0% (95% confidence interval or CI [65.5, 70.4]), 68.6% [65.1%, 72.2%], and 69.4% (95% CI [66.9%, 71.9%], respectively. The EDP model had a c-index of 75.1% (95% CI [71.3, 79.0]).

Conclusions: We introduce a contemporary RCC recurrence model built and internally validated using prospective and highly annotated data from a clinical trial. Performance characteristics of the current model exceed available prognostic models with the added benefit of being histology inclusive and TNM agnostic.

Patient summary: Important decisions, including treatment protocols, clinical trial eligibility, and life planning, rest on our ability to predict cancer outcomes accurately. Here, we introduce a contemporary renal cell carcinoma prognostic model leveraging high-quality data from a clinical trial. The current model predicts three outcome measures commonly utilized in clinical practice and exceeds the predictive ability of available prognostic models.

Keywords

Renal cell carcinoma; Prognostic model; Disease-free survival; ASSURE trial

1. Introduction

The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system has been the foundation for cancer risk stratification since its introduction in 1977 [1]. While TNM staging provides an excellent framework for cancer communication and standardization, it has limited ability to provide an individualized risk assessment. As a result, clinicopathological prognostic models have been introduced to aid in individual

prognostication. In renal cell carcinoma (RCC), the adoption of clinicopathological models has been swift, becoming the pillars of risk stratification: dictating guideline development and clinical trial eligibility.

Currently, eight prognostic algorithms and nomograms [2–10] are commonly used to predict RCC outcomes following complete local resection. A recent validation [11] of these models, using contemporary data, demonstrated a significant reduction of their previously published and validated predictive indices. A principal factor often overlooked with the existing prediction models is the inherent reliance on retrospective data for their development and respective validations. The use of retrospective data is prone to source and reporting biases due to differences in data collection techniques, a lack of standardized outcome and histological reporting, and cohorts that span several decades. Moreover, each of the available models [2–10] offers a prediction on a single oncological outcome, and tends to be histology focused and TNM edition dependent, limiting its applicability in contemporary cohorts.

We introduce a contemporary prognostic model for patients with intermediate- and high-risk localized RCC, with an emphasis on clinical applicability (histology inclusive, with reporting of three distinct outcomes) and generalizability (TNM agnostic) to current and future cohorts, by leveraging highly annotated, centrally reviewed outcome data from the phase III adjuvant ECOG-ACRIN 2805 (ASSURE) [12] clinical trial.

2. Patients and methods

2.1. Study population

Our study population consists of patients recruited and followed in the ECOG-ACRIN 2805 (ASSURE) adjuvant RCC trial [12], which assessed the efficacy of adjuvant targeted therapy (sunitinib and sorafenib) in patients with fully resected intermediate- and high-risk localized kidney cancer (pT1b and G3–4; pT2/pT3/pT4; N1) [12]. All pathological specimens were centrally reviewed. Patients were followed for recurrence per protocol until disease recurrence or through 10 yr. Accrual to ASSURE was completed in September 2010, with recurrence data collected through February 2020. The median (Q1, Q3) follow-up among patients who are alive was 9.6 (7.7, 10.0) yr.

2.2. Statistical analyses

2.2.1. Model outcome measures—Three endpoints of interest were chosen for model development: disease-free survival (DFS), overall survival (OS), and early disease progression (EDP). DFS was defined as the time from randomization to disease recurrence (including local and distant recurrences), development of a second primary cancer (excluding localized breast, localized prostate, and nonmelanoma cancer), or death from any cause. OS was defined as the time from randomization to death from any cause. For DFS and OS endpoints, patients who are alive were censored at the date of the last contact. EDP was defined as a DFS event within 1 yr of randomization; patients censored for DFS within this time frame were not considered to have had EDP.

2.2.2. Cohort development—A total of 1943 patients were included in the trial. Patients with collecting duct carcinoma ($n = 1$) and those without central pathology data (n

= 207) were excluded from the study (CONSORT diagram, Supplementary Fig. 1). Patients were split into training and validation sets for the primary outcome measure (DFS). Several data splitting methods were considered (see the Supplementary material), but given the multi-institutional nature of the ASSURE trial and concern for outcome reporting bias [13], a nonrandom split was performed. The whole cohort was used for the secondary outcome measures (OS and EDP) due to the limited number of events for each outcome.

2.2.3. Modeling approach—A review of survival data demonstrated nonproportionality hazards for several important predictors precluding a Cox proportional hazard (PH) model. Several modeling strategies were evaluated (see the Supplementary material), and a parametric log-normal accelerated failure time (AFT) model was chosen as most appropriate for the DFS and OS endpoints. An AFT model differs from the standard PH models in that the risk factor impacts the time for the event to occur, whereas in PH models, the risk factor impacts the hazard of an event occurring. For the EDP outcome, a multivariable binary logistic regression was fitted to model the log odds. For each of the outcomes, the multivariable model building strategy placed emphasis on optimality, parsimony, and simplicity (see the Supplementary material). A variable is included in the final model if it contributes ≥1% increase in discrimination performance.

For ease of clinical implementation, points were assigned to each selected variable (based on the multivariable model's regression coefficient). Risk groups were defined based on the natural separation in the survival curve of the weighted points (see the Supplementary material). Missing data imputation was not attempted, and cases with missing values for factors in any model were excluded from analyses (case-wise deletion).

2.2.4. Model performance, fit, sensitivity, and validation assessments—Model performance was assessed using discrimination [14,15] and calibration tests (see the Supplementary material). Decision curve analysis was performed for each outcome (see the Supplementary material). Variable-wise and global tests were used to assess model fit (see the Supplementary material), and sensitivity analyses were performed under different scenarios (see the Supplementary material). In the training set, estimates were reported for model performance metrics, and a bootstrap approach (with 10K samples) was used to assess bias in model parameter and coefficient estimates. In the DFS validation dataset, the regression coefficients obtained from the training model were applied as weights to each corresponding variable in the validation dataset. The risk score (linear predictor) was calculated from which performance metrics were assessed. Model development and interval validation adhered strictly to the TRIPOD guidelines [16].

3. Results

3.1. Cohort characteristics

A total of 1735 patients were utilized in the analysis (Table 1). The mean tumor size was 8.7 ± 3.5 cm. More than half of the patients (62.7%) reported tumor-related symptoms on presentation (43.6% locally and 19.1% systemically). The majority of tumors were clear cell RCC (79.8% per local and 81.3% per central review) of high grade (65.5%; nuclear grades 3 and 4), with 41.9% exhibiting tumor necrosis and 8.5% presenting with nodal involvement.

The median OS has not been reached, while the median DFS was 7.5 yr (95% confidence interval or CI [6.5-8.5]; Table 1).

3.2. DFS prognostic model

For the DFS model, patients were split into training (1139) and validation (596) cohorts based on the reporting of hospital sites and oncology groups to control for variations in outcome reporting. The training and validation cohorts were balanced with respect to the variables included in the final model, median follow-up, outcome events, and treatment assignment (Table 1). Following the evaluation of each potential modeling variables (Supplementary Table 1), six (vascular invasion, tumor histology, tumor size, tumor grade, presence of tumor necrosis, and presence of nodal disease) were included in the final prognostic model for DFS. The factors selected were based on a substantial (≥1%) increase in the model's discriminatory ability (c-index). Points were assigned to each risk factor based on the regression estimates (Table 2), and we created three risk groups (low, intermediate, and considerable risk), noting excellent separation in the Kaplan-Meier curve (Fig. 1A). The predictive concordance of the DFS model was 78.4% at 6 mo and 74.5% at 1 yr. The model was found to have time-dependent degradation of its predictive ability, with a global c-index of 68.0% (95% CI [65.5, 70.4]; Fig. 2). The global c-index of the DFS model in the validation cohort is 68.6% (65.1, 72.2). The DFS model was well calibrated (with an observed Brier score of 0.17) across several time points, increasing accuracy at longer follow-ups (Supplementary Fig. 4).

3.3. OS prognostic model

Six factors were included in the final OS model: age at diagnosis, tumor histology, tumor size, tumor grade, presence of tumor necrosis, and presence of nodal disease. As with DFS, points were assigned to each of the six variables (Table 2), and four risk groups (low, favorable intermediate, unfavorable intermediate, and considerable risk) were created based on the natural separation in the Kaplan-Meier curve (Fig. 1B). The 1- and 5-yr predictive c-indexes for OS of the model were 81.9% and 72.2%, respectively. The model's predictive ability also degraded over time with a global c-index of 69.4% (95% CI [66.9, 71.9]; Fig. 2).

3.4. EDP model

A total of 258 (15.0 %) patients experienced a DFS event within the 1st year of randomization, which constituted 29.1% of all DFS events (258/887; see Supplementary Fig. 10). When all available factors were analyzed, six were included in the final model: sarcomatoid features, tumor histology, tumor size (≥7.0 vs <7.0 cm), tumor grade, necrosis, and presence of nodal disease (Table 2). The calculated area under the curve for the final EDP model was 75.1% (95% CI [71.3, 79.0]; Fig. 2B).

3.5. Sensitivity analyses

Sensitivity analyses were conducted for eight different scenarios (Supplementary material), of which two are clinically relevant.

Papillary histology subclassification (type 1 vs type 2) was not performed consistently at individual sites but was recorded during the centralized review. The final model was

based on site-specific histology to be more representative of clinical practice. Following the sensitivity analysis comparing site versus centralized review (scenarios #3 and #4), there was no substantial change in the model's discriminatory ability.

Given the adjuvant nature of the trial, changes in model performance by treatment subset (placebo, sunitinib, and sorafenib) were analyzed. There was some heterogeneity in model performance between treatment arms, most notable in the OS outcome. For this endpoint, the maximum absolute difference in global c-index between the pooled population and each treatment arm was 2.9%. Model discrimination was more homogeneous for DFS and EDP models, with a maximum absolute difference of 1.3% and 1.6%, respectively.

4. Discussion

The development and implementation of robust clinical prognostic models have gained significant popularity due to the inherent limitations of standard TNM staging. As a result, the AJCC has recently recognized and included several personalized probabilistic predictors in their staging recommendations [17]. In RCC, none of the available models [2–10] have been endorsed by the AJCC, mainly due to their reliance on retrospective data. Here, we introduce a contemporary RCC prognostic model developed with an emphasis on clinical applicability (DFS, OS, and EDP) and generalizability (TNM agnostic) by leveraging outcome data from the largest adjuvant (ECOG-ACRIN 2805; ASSURE) [12] RCC trial reported to date.

The present model was developed to provide an individualized DFS estimate since it encapsulates most, if not all, of other failure time endpoints. Six factors were found to have a significant impact (≥1%) on the discriminatory ability (c-index) of the model (vascular invasion, tumor histology, tumor size, tumor grade, presence of tumor necrosis, and presence of nodal disease). Other risk factors such as adrenalectomy status, renal sinus invasion, age at diagnosis, and sarcomatoid features were also found to be significantly associated with the outcome in multivariate analysis; however, the inclusion of these variables in the model provided only a slight improvement (1.6%) in the model's discriminatory ability (c-index). In keeping with a model-building strategy for ease in clinical implementation, the decision was made to limit the model to the six most discriminatory variables. Of the six factors, tumor histology was found to be the strongest predictor of DFS (clear cell, papillary type II, mixed papillary, or variant histology >25% clear cell: AF 0.21 [95% CI {0.12–0.34}] and unclassified or <25% clear cell: AF 0.14 [95% CI {0.07–0.29}]) followed by the presence of nodal metastases (AF 0.36 [95% CI {0.25–0.53}]). The overall predictive ability of the DFS model was 74.5% at 1 yr compared with 64.8% for TNM. Similar to other models [11], the current model also shows degradation of its predictive ability over time, with the global c-indexes of the model of 68.0% (95% CI [65.5–70.4]) and 68.6% (95% CI [65.1%, 72.2%]) in the development and validation cohorts, respectively.

In addition to DFS, separate models were created for OS and EDP. The addition to these secondary outcome measures was thought to be important for patient counseling and clinical trial design. The OS model consisted of six variables, similar to those in DFS, with the exception that age replaced vascular invasion as a significant predictor. The OS

model's overall discriminatory ability was calculated at 69.4% (95% CI [66.9%, 71.9%]). Importantly, this outperforms the only currently available OS model in RCC (UISS [4]), which had a predictive ability of 56% (95% CI 55.5–55.7) when validated in a prospective dataset [11].

EDP, defined as a DFS event within 12 mo, was also considered due to its increasing importance in RCC clinical trial design and its ability to potentially affect surveillance protocols. It has been postulated that heterogeneity in eligibility criteria might explain the difference in findings between the ASSURE, ATLAS, and PROTECT trials, all of which failed to note a statistical difference in primary or secondary endpoints, and the S-TRAC trial that noted improved progression-free survival with adjuvant sunitinib leading to Food and Drug Administration (FDA) approval [18]. The reliance on guideline recommendations for RCC surveillance has come into question [19], advocating for a risk-based approach [20]. The EDP model provided the best predictive ability of all presented models, with an overall c-index of 75.1% (95% CI 71.3–79.0), and it would provide an ideal tool to help stratify patients into high-intensity follow-up. Interestingly, the presence of sarcomatoid features (odds ratio 2.23 [95% CI 1.48–3.37]) was an important predictor of early recurrence, with a significant degradation in its predictive ability over time, limiting its impact in the DFS and OS models. As a result, patients with sarcomatoid features should be followed with aggressive surveillance protocols and be considered for adjuvant clinical trials.

The presented model allows for individualized risk estimation and clinical stratification of each into risk categories (Fig. 3). Risk estimates for DFS and OS can then be either calculated using the log-normal distribution survival function formula (Supplementary material) embedded in the web-based calculator (https://studies.fccc.edu/nomograms/492) or estimated based on the risk groups identified in the Kaplan-Meier analysis (Fig. 3). Notably, both DFS and OS models demonstrate a time-dependent degradation [21,22] (Fig. 2). The treating clinician must be cognizant of this phenomenon and assert prediction confidence, respectively, when communicating conditional survival estimates (eg, 2 vs 5 vs 10 yr).

The present model outperforms all currently available prediction models, including TNM in several aspects: first, it provides improved or comparable discriminatory indices for cancer-specific survival (CSS; 68.6%; 95% CI [65.1%, 72.2%]) and OS (69.4%; 95% CI [66.9%, 71.9%]) of any model currently utilized in guideline development and clinical trial design. In our prior validation of the established retrospective models [11], the discriminatory indices of the three most commonly utilized models UISS [4] (OS), Leibovich [5] (metastasis-free survival), and SSIGN [6] (CSS) were noted to be 56.0%, 62.5%, and 68.8%, respectively. While the SSIGN model had a comparable discriminatory ability, the model is limited to clear cell histology only and dependent on 1997 TNM staging. The current model is applicable to patients with both clear cell RCC and non–clear cell RCC histologies, provides three clinically valuable outcomes measures (DFS, OS, and EDP), and is TNM stage agnostic, allowing for increased flexibility in clinical application and generalization into future cohorts.

The present model is not without limitations. As with all predictive models [11], ours demonstrates a significant degradation of its discriminatory performance (for DFS and OS) over time (Fig. 1A), which also reflects decreasing event rates [7]. Furthermore, the data utilized for model training and validation resulted from an adjuvant trial that sought to assess the role of targeted adjuvant therapy in patients at intermediate and high risks of recurrence, which poses a risk for potential biases. First is the risk of selection bias due to the stringent inclusion criteria associated with clinical trials (age, performance status, and surgical candidacy), which may affect its discriminatory indices when validated in a general population. Second, there was evidence of model performance heterogeneity between treatment groups (placebo vs treatment), most notable in the OS model (c-index difference 2.9%), likely related to nonrandom occurrence and limited events. Third, the outcome data utilized were based on patients at intermediate and high risks of experiencing a postsurgical recurrence; as such, the model should be utilized in that context and avoided in those with a negligible risk of recurrence (pT1a G1–4, pT1b G1–2). Lastly, the validation performed was internal, so we cannot exclude the possibility of model overfitting due to variable and threshold selection.

5. Conclusions

We report a contemporary RCC recurrence model, developed and validated using prospective and highly annotated clinical trial data, with an emphasis on clinical applicability. The current model exceeds the predictive ability of currently available prognostic models. Pending external validation, this model should serve as the standard for future risk communication and trial design eligibility in patients with intermediate- and high-risk RCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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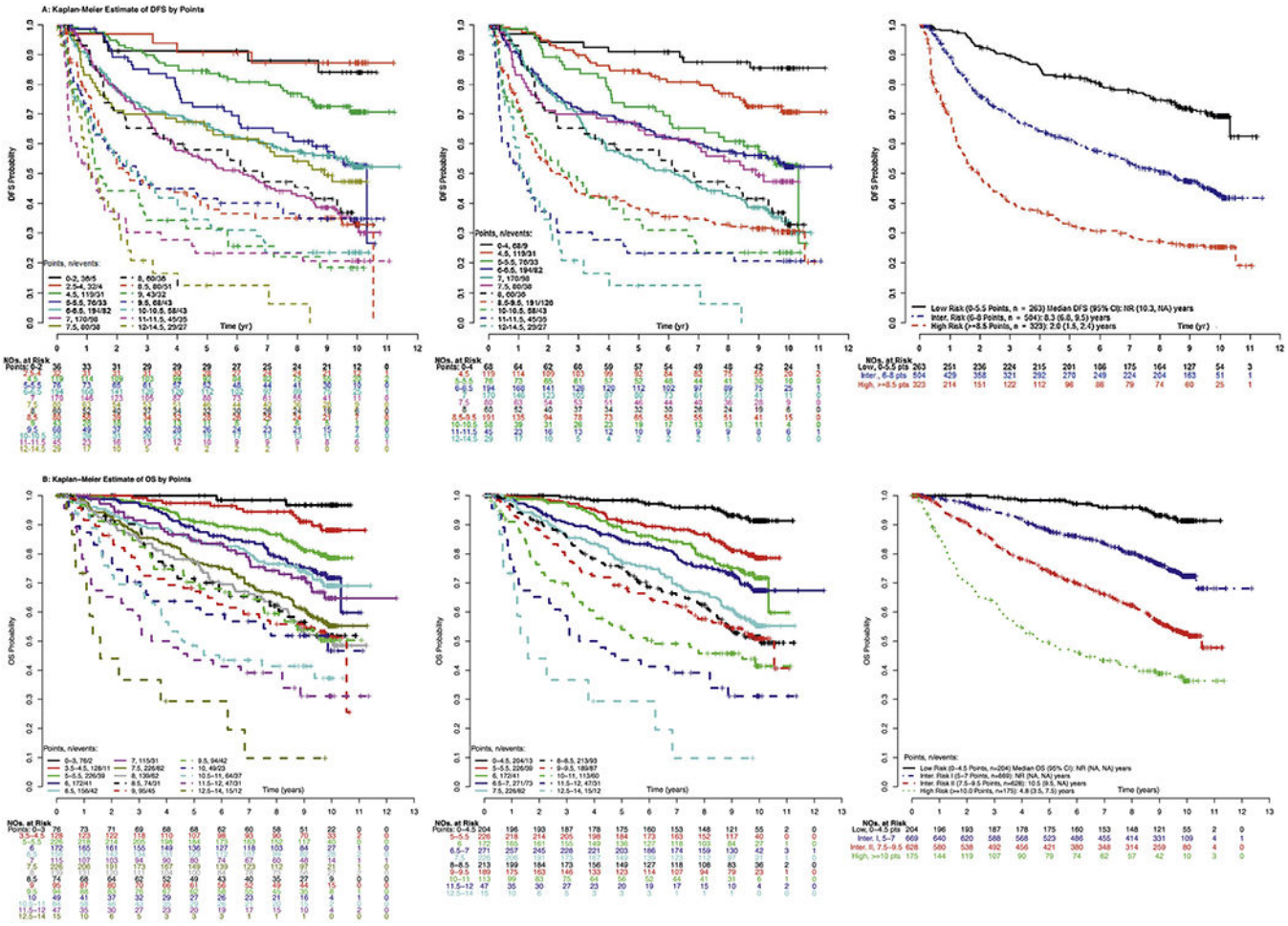

Fig. 1 –.

Kaplan-Meier curves for (A) DFS risk groups and (B) OS risk groups. CI = confidence interval DFS = disease-free survival; NA = not available; NR = not reached; OS = overall survival.

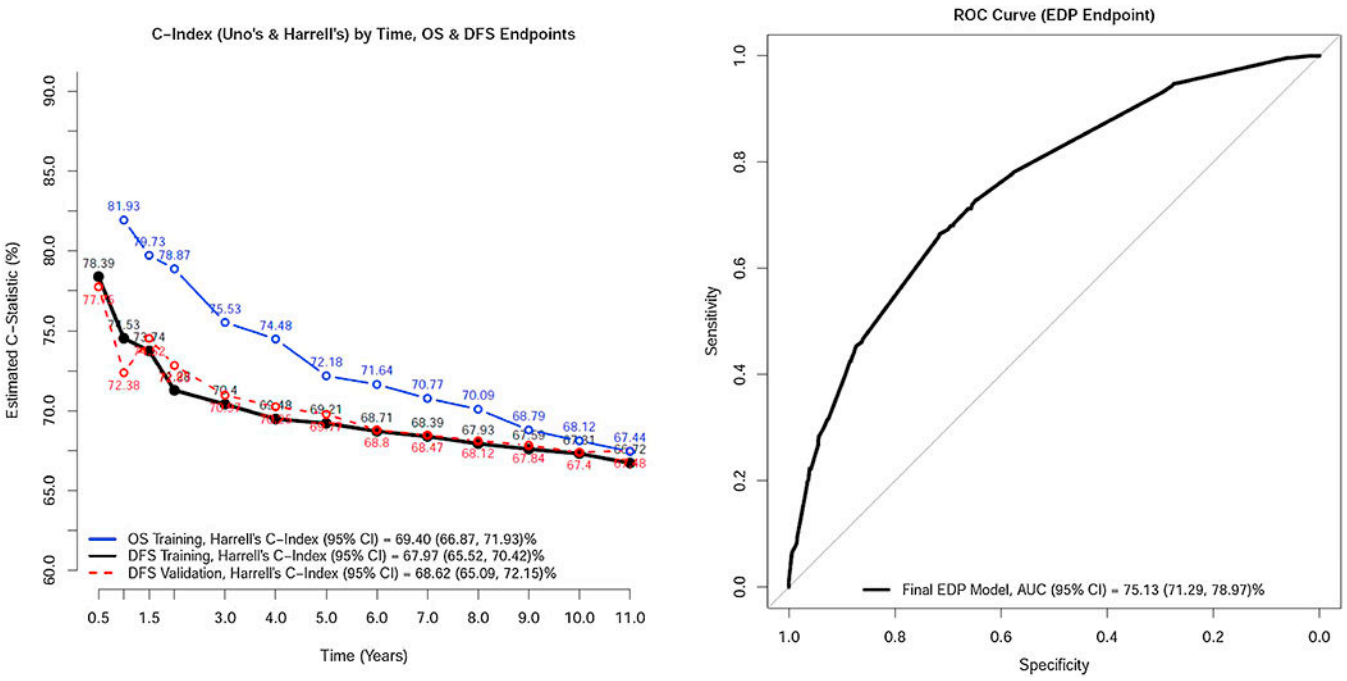

Fig. 2 –.

Model discrimination measures. AUC = area under the curve; CI = confidence interval; DFS = disease-free survival; EDP = early disease progression; OS = overall survival; ROC = receiver operating characteristics.

A

Risk Factors	DFS Points	OS Points
Vascular Invasion, ref = Intra/renal/IVC vs None	1.0	NA
Age at RCC Diagnosis (years), ref = ≤ 51.0		
>51.0 ≤ 60.0	NA	1.0
> 60.0		2.0
[a]Renal Histology, ref = Chromophobe or Pap. Type 1		
Clear Cell (CC), Papillary Type II, Mixed Papillary, or variant histology >25% CC	4.5	4.0
Unclassified or < 25% CC	5.5	4.5
Tumor Size (cm), ref = ≤7.0		
>7.0 ≤10.0	1.5	1.5
>10.0	2.5	2.0
Fuhrman Grade, Grade 4 vs Grade 1-3	2.0	2.0
Coagulative Necrosis, Yes vs No	1.5	1.5
Regional Lymph Nodes (pN), pN1/2 vs pN0/X	3.0	2.5

B

Risk Group	Disease Free Survival Estimate (%)			
	1-year	2-year	5-year	10-year
Low Risk (0-5.5 points)	98.1	92.6	82.6	69.3
Intermediate risk (6-8 points)	89.7	76.2	61.1	42.3
High Risk (≥8.5 points)	68.9	49.2	33.1	25.3

C

Risk Group	Overall Survival Estimate (%)			
	1-year	2-year	5-year	10-year
Low Risk (0-4.5 points)	100.0	100.0	98.4	91.4
Favorable Intermediate risk (5-7 points)	99.1	97.2	87.7	72.3
Unfavorable Intermediate risk (7.5-9.5 points)	96.5	90.7	73.8	52.6
High Risk (≥10 points)	85.5	70.6	49.0	36.3

D

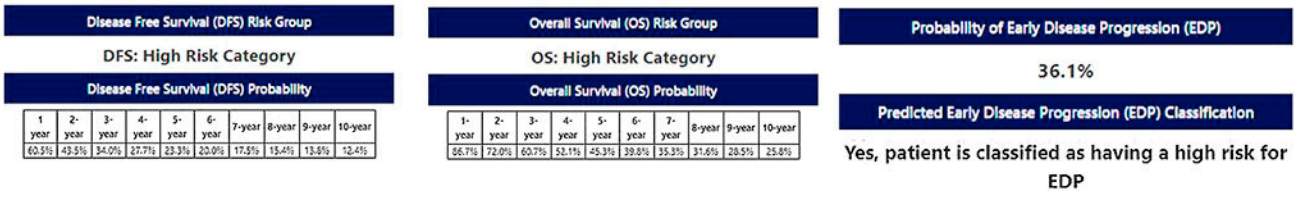

Fig. 3 –.

(A) Points associated with each risk factor, (B) estimated disease-free survival, (C) estimated overall survival based on risk groups, and (D) output from online calculator. CC = clear cell; DFS = disease-free survival; EDP = early disease progression; IVC = inferior vena cava; NA = not available; OS = overall survival; RCC = renal cell carcinoma. [a] If tumor's papillary histology cannot be differentiated into type I, II, or mixed, the model user should use the points assigned to clear cell or papillary type II/mixed or >25% CC category. * A 55-yr-old male with a 12-cm clear cell RCC (grade 2), with evidence of renal parenchyma invasion, tumor necrosis, and node-positive disease, would be in the high-risk group for both DFS and OS, and therefore have estimated 5-yr DFS and OS probabilities of 33.1% and 49.0%, respectively. Alternatively, the web-based calculator can be used (https://studies.fccc.edu/nomograms/492).

Table 1 –

Demographic, baseline, and clinicopathological factors

Variables	Frequency (%)		
	Full cohort (1735, 100%)	Training set (1139, 65.6%)	Validation set (596, 34.4%)
Demographic factors			
Age at RCC diagnosis (yr), median (Q1, Q3)	56 (48, 63)	56 (49, 63)	56 (48, 64)
Age at RCC diagnosis categories (yr)			
≥18–≤51	599 (34.5)	396 (34.8)	203 (34.1)
>51–≤60	549 (31.6)	362 (31.8)	187 (31.4)
>60	587 (33.8)	381 (33.4)	206 (34.5)
Sex			
Male	1172 (67.6)	765 (67.2)	407 (68.3)
Female	563 (32.4)	374 (32.8)	189 (31.7)
Race			
Black	75 (4.3)	49 (4.3)	26 (4.4)
Hawaiian	1 (0.1)	1 (0.1)	–
Native American	10 (0.6)	7 (0.6)	3 (0.5)
Asian	36 (2.1)	21 (1.8)	15 (2.5)
White	1586 (91.4)	1047 (91.9)	539 (90.4)
Missing/not reported	27 (1.6)	14 (1.2)	13 (2.2)
Ethnicity			
Hispanic	88 (5.1)	43 (3.8)	45 (7.6)
Non-Hispanic	1532 (88.3)	1015 (89.1)	517 (86.7)
Missing/not reported	115 (6.6)	81 (7.1)	34 (5.7)
Baseline/on study factors			
Symptomatic presentation (how was disease discovered?)			
Incidental	647 (37.3)	414 (36.4)	233 (39.1)
Locally symptomatic	756 (43.6)	503 (44.2)	253 (42.4)
Systemically symptomatic	331 (19.1)	221 (19.4)	110 (18.5)
Missing	1	1	–
ECOG performance status			
0	1389 (81.6)	907 (81.1)	482 (82.5)
1	313 (18.4)	211 (18.9)	102 (17.5)
Missing	33	21	12
History of cardiovascular disease			
No	1332 (76.8)	896 (78.7)	436 (73.2)
Yes	402 (23.2)	242 (21.3)	160 (26.8)
Missing	1	1	–
History of thromboembolic event			
No	1666 (96.1)	1098 (96.5)	568 (95.3)
Yes	68 (3.9)	40 (3.5)	28 (4.7)
Missing	1	1	–

Variables	Frequency (%)		
	Full cohort (1735, 100%)	Training set (1139, 65.6%)	Validation set (596, 34.4%)
Clinical N stage			
cN0	1575 (91.6)	1036 (91.8)	539 (91.2)
cN1	77 (4.5)	52 (4.6)	25 (4.2)
cN2	67 (3.9)	40 (3.6)	27 (4.6)
Missing	16	11	5
Clinical T stage			
cT0	17 (1.0)	12 (1.1)	5 (0.8)
cT1a	29 (1.7)	16 (1.4)	13 (2.2)
cT1b	204 (11.8)	133 (11.7)	71 (11.9)
cT2	535 (30.9)	343 (30.1)	192 (32.2)
cT3a	487 (28.1)	335 (29.4)	152 (25.5)
cT3b	428 (24.7)	280 (24.6)	148 (24.8)
cT3c	15 (0.9)	9 (0.8)	6 (1.0)
cT4	19 (1.1)	10 (0.9)	9 (1.5)
Missing	1	1	–
Surgical factors (local, site determined)			
Nuclear grade			
1	42 (2.4)	32 (2.8)	10 (1.7)
2	550 (32.0)	363 (32.2)	187 (31.6)
3	796 (46.3)	507 (45.0)	289 (48.8)
4	330 (19.2)	224 (19.9)	106 (17.9)
Missing	17	13	4
Renal histology			
Conventional clear cell	1385 (79.8)	912 (80.1)	473 (79.4)
Papillary	136 (7.8)	88 (7.7)	48 (8.1)
Chromophobe	95 (5.5)	67 (5.9)	28 (4.7)
Mixed, >25% clear cell	47 (2.7)	25 (2.2)	22 (3.7)
Mixed, <25% clear cell	24 (1.4)	17 (1.5)	7 (1.2)
Unclassified	48 (2.8)	30 (2.6)	18 (3.0)
Primary tumor stage (pT)			
pT1a	6 (0.3)	3 (0.3)	3 (0.5)
pT1b	166 (9.6)	113 (9.9)	53 (8.9)
pT2	467 (26.9)	312 (27.4)	155 (26.0)
pT3a	588 (33.9)	391 (34.3)	197 (33.1)
pT3b	473 (27.3)	301 (26.4)	172 (28.9)
pT3c	16 (0.9)	9 (0.8)	7 (1.2)
pT4	19 (1.1)	10 (0.9)	9 (1.5)
Regional lymph nodes (pN)			
NO/X	1588 (91.5)	1043 (91.6)	545 (91.4)
N positive	147 (8.5)	96 (8.5)	51 (8.5)
Was adrenalectomy performed?			

Variables	Frequency (%)		
	Full cohort (1735, 100%)	Training set (1139, 65.6%)	Validation set (596, 34.4%)
No	946 (55.5)	642 (57.1)	304 (52.3)
Yes, full	613 (35.9)	381 (33.9)	232 (39.9)
Yes, partial	147 (8.6)	102 (9.1)	45 (7.7)
Missing	29	14	15
Kidney embolization performed?			
No	1576 (88.8)	797 (87.8)	462 (90.6)
Yes	159 (11.2)	111 (12.2)	48 (9.4)
Missing	317	231	86
Was a lymphadenectomy performed?			
No	1117 (64.4)	754 (66.2)	363 (60.9)
Yes	618 (35.6)	385 (33.8)	233 (39.1)
Type of surgery			
Partial nephrectomy	92 (5.3)	63 (5.5)	29 (4.9)
Radical nephrectomy	1643 (94.7)	1076 (94.5)	567 (95.1)
Surgical margin resection status			
R0 (all margins pathologically −ve)	1592 (91.8)	1058 (92.9)	534 (89.6)
R1 (microscopically +ve margins/microscopic residual disease)	7 (0.4)	4 (0.4)	3 (0.5)
R2 (macroscopically +ve margins/gross residual disease)	3 (0.2)	1 (0.1)	2 (0.3)
RX (residual dx cannot be assessed)	1 (0.1)	0 (0.0)	1 (0.2)
R0.5 (path, −ve, thrombus +ve at renal vein)	132 (7.6)	76 (6.7)	56 (9.4)
Presence of sarcomatoid features?			
No	1578 (91.2)	1039 (91.4)	539 (90.7)
Yes	153 (8.8)	98 (8.6)	55 (9.3)
Missing	4	2	2
Surgical approach			
Laparoscopic	744 (42.9)	513 (45.0)	231 (38.8)
Open	991 (57.1)	626 (55.0)	365 (61.2)
Which kidney was affected/operated on?			
Left	885 (51.0)	579 (50.8)	306 (51.3)
Right	847 (48.8)	558 (49.0)	289 (48.5)
Bilateral	3 (0.2)	2 (0.2)	1 (0.2)
Gross disease extent			
Multifocal	123 (7.5)	80 (7.4)	43 (7.7)
Unifocal	1512 (92.5)	997 (92.6)	515 (92.3)
Missing	100	62	38
Radiological findings of contralateral kidney			
Abnormal	126 (7.3)	80 (7.0)	46 (7.7)
Normal	1606 (92.7)	1057 (93.0)	549 (92.3)
Missing	3	2	1
Were there postoperative/early complications?			

Variables	Frequency (%)		
	Full cohort (1735, 100%)	Training set (1139, 65.6%)	Validation set (596, 34.4%)
No	1476 (86.0)	975 (86.7)	501 (84.6)
Yes	241 (14.0)	150 (13.3)	91 (15.4)
Missing	18	14	4
Pathological factors (centrally reviewed by EA)			
Tumor size (cm), median (Q1, Q3)	8.0 (6.2, 10.5)	8.0 (6.3, 10.4)	8.3 (6.0, 10.8)
Tumor size categories (cm)			
≤7.0	582 (33.9)	379 (33.7)	203 (34.3)
>7.0–≤10.0	670 (39.0)	452 (40.2)	218 (36.9)
>10	464 (27.1)	294 (26.1)	170 (28.8)
Missing	19	14	5
Tumor invasion			
Capsule intact	1064 (62.8)	694 (62.4)	370 (63.7)
Invading perirenal fat	604 (35.7)	401 (36.1)	203 (34.9)
Invading beyond Gerota’s fascia	13 (0.8)	8 (0.7)	5 (0.9)
Invading other structures	12 (0.7)	9 (0.8)	3 (0.5)
Missing	42	27	15
Vascular invasion			
None seen	1050 (61.0)	700 (61.8)	350 (59.4)
Intrarenal	136 (7.9)	81 (7.1)	55 (9.3)
Renal	505 (29.3)	331 (29.2)	174 (29.5)
IVC, subdiaphragmatic	25 (1.5)	17 (1.5)	8 (1.4)
IVC, supradiaphragmatic	6 (0.3)	4 (0.4)	2 (0.3)
Missing	13	6	7
Sarcomatoid features			
No	1544 (91.9)	1028 (92.4)	516 (90.8)
Yes	137 (8.1)	85 (7.6)	52 (9.2)
Missing	54	26	28
Coagulative necrosis			
No	991 (58.1)	641 (57.0)	350 (60.1)
Yes	716 (41.9)	484 (43.0)	232 (39.9)
Missing	28	14	14
Renal sinus invasion			
Absent	1192 (68.9)	791 (69.5)	401 (67.6)
Pelvic vein	128 (7.4)	87 (7.6)	41 (6.9)
Pelvic stroma	223 (12.9)	147 (12.9)	76 (12.8)
Both pelvic vein and stroma	188 (10.9)	113 (9.9)	75 (12.6)
Missing	4	1	3
Histology			
Clear cell	1276 (81.3)	840 (81.9)	436 (80.1)
Chromophobe	123 (7.8)	79 (7.7)	44 (8.1)
Unclassified	29 (1.8)	16 (1.6)	13 (2.4)

Variables	Frequency (%)		
	Full cohort (1735, 100%)	Training set (1139, 65.6%)	Validation set (596, 34.4%)
Papillary, type I	54 (3.4)	33 (3.2)	21 (3.9)
Papillary, type II	80 (5.1)	52 (5.1)	28 (5.1)
Papillary, type mixed	8 (0.5)	6 (0.6)	2 (0.4)
Other [a]			
Non-RCC histology	44	32	12
Mixed histology	116	79	37
Missing	5	2	3
Outcomes and study-related variables			
Disease-free survival			
Number of events	887	586	301
Median DFS (95% CI), yr	7.5 (6.5, 8.5)	7.5 (6.6, 8.6)	7.0 (5.5, 9.1)
Median FU (Q1, Q3), yr	9.5 (6.4, 10.0)	9.6 (7.8, 10.0)	9.2 (5.5, 10.0)
Overall survival			
Number of events	549	355	194
Median OS (95% CI), yr	NR (NA, NA)	NR (NA, NA)	NR (NA, NA)
Median FU (Q1, Q3), yr	9.6 (7.7, 10.0)	9.7 (8.5, 10.0)	9.4 (6.0, 10.0)
Early disease progression			
No	1461 (85.0)	969 (85.8)	492 (83.4)
Yes	258 (15.0)	160 (14.2)	98 (16.6)
Missing	16	10	6
Treatment arm			
Ann A (sunitinib)	575 (33.1)	383 (33.6)	192 (32.2)
AnnB (sorafenib)	579 (33.4)	384 (33.7)	195 (32.7)
Ann C (placebo)	581 (33.5)	372 (32.7)	209 (35.1)
NCTN group			
ECOG-ACRIN	668 (38.5)	668 (58.6)	–
RTOG	16 (0.9)	–	16 (2.7)
NCCTG	36 (2.1)	–	36 (6.0)
CALGB	282 (16.3)	282 (24.8)	–
CCTG	119 (6.9)	119 (10.4	–
SWOG	504 (29.0)	–	504 (84.6)
NSABP	70 (4.0)	70 (6.1)	–
ACOSOG	8 (0.5)	–	8 (1.3)
CTSU	26 (1.5)	–	26 (4.4)
ALLIANCE	4 (0.2)	–	4 (0.7)
NRG	2 (0.1)	—	2 (0.3)

CI = confidence interval; DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; FU = follow-up among patients without events; IVC = inferior vena cava; NA = not applicable/available; OS = overall survival; RCC = renal cell carcinoma; NCTN = National Clinical Trials Network; NR = not reached.

[a] These numbers were obtained from a free text field and should be regarded as rough estimates.

Table 2 –

DFS, OS, and EDP multivariable regression estimates

Risk factors	DFS endpoint (nonmissing, *n* = 1090)				OS endpoint (nonmissing, *n* = 1676)				EDP endpoint (nonmissing, *n* = 1662)		
	Beta ± SE	AF (95% CI)	Wald chi-square, df	Points	Beta ± SE	AF (95% CI)	Wald chi-square, df	Points	Beta ± SE	OR (95% CI)	Wald chi-square, df
Vascular invasion, ref = intra/renal/IVC vs none	−0.36 ± 0.11	0.70 (0.56, 0.87)	10.16, 1	1.0							
Age at RCC diagnosis (yr), ref = ≤51.0											
>51.0–≤60.0					−0.31 ± 0.10	0.73 (0.60, 0.90)	8.75, 1	1.0			
>60.0					−0.57 ± 0.10	0.57 (0.46, 0.69)	30.81, 1	2.0			
Sarcomatoid features, yes vs no									0.80 ± 0.21	2.23 (1.48, 3.37)	14.69, 1
Renal histology [a], ref = chromophobe or pap. type 1											
Clear cell or pap. type II/pap mixed or variant histology >25% CC	−1.58 ± 0.26	0.21 (0.12, 0.34)	36.88, 1	4.5	−1.21 ± 0.22	0.30 (0.19, 0.46)	30.55, 1	4.0	1.40 ± 0.47	4.07 (1.61, 10.27)	8.82, 1
Unclassified or < 25% CC	−1.98 ± 0.37	0.14 (0.07, 0.29)	27.93, 1	5.5	−1.44 ± 0.29	0.24 (0.13, 0.42)	24.67, 1	4.5	1.92 ± 0.55	6.80 (2.31, 20.02)	12.09, 1
Tumor size (cm), ref = ≥7.0											
>7.0–≤10.0	−0.47 ± 0.13	0.63 (0.48, 0.81)	12.5, 1	1.5	−0.39 ± 0.10	0.68 (0.56, 0.82)	15.31, 1	1.5			
>10.0	−0.82 ± 0.15	0.44 (0.33, 0.59)	31.27, 1	2.5	−0.62 ± 0.11	0.54 (0.44, 0.66)	33.05, 1	2.0			
Tumor size (cm), ≥7.0 vs <7.0									0.62 ± 0.17	1.86 (1.32, 2.61)	12.79, 1
Nuclear grade, grade 4 vs grade 1–3	−0.75 ± 0.14	0.47 (0.36, 0.62)	30.3, 1	2.0	−0.58 ± 0.10	0.56 (0.46, 0.68)	34.01, 1	2.0	0.57 ± 0.18	1.77 (1.24, 2.54)	9.80, 1
Coagulative necrosis, yes vs no	−0.62 ± 0.12	0.54 (0.43, 0.68)	28.49, 1	1.5	−0.54 ± 0.09	0.58 (0.49, 0.69)	39.52, 1	1.5	0.88 ± 0.16	2.42 (1.78, 3.30)	31.51, 1
Regional lymph nodes (pN), pN1/2 vs pNO/X	−1.02 ± 0.19	0.36 (0.25, 0.53)	27.69, 1	3.0	−0.84 ± 0.13	0.43 (0.33, 0.56)	38.94, 1	2.5	0.94 ± 0.22	2.57 (1.68, 3.92)	19.09, 1
DFS/OS AFT (log-normal) model parameters											
Mean (μ) ± SE	4.4738 ± 0.28		2.54e2, 1		4.9741 ± 0.25		3.87e2, 1				
Scale (σ) ± SE	1.6198 ± 0.05		9.48e2, 1		1.3070 ± 0.04		8.59e2, 1				

Risk factors	DFS endpoint (nonmissing, *n* = 1090)				OS endpoint (nonmissing, *n* = 1676)				EDP endpoint (nonmissing, *n* = 1662)		
	Beta ± SE	AF (95% CI)	Wald chi-square, df	Points	Beta ± SE	AF (95% CI)	Wald chi-square, df	Points	Beta ± SE	OR (95% CI)	Wald chi-square, df
EDP model intercept ± SE									−4.4059 ± 0.50	0.01 (>0, 0.03)	78.3, 1
c-Statistic (DFS & OS)/AUC (EDP) ± boot SE (95% CI)	67.97 ± 1.25 (65.52, 70.42)				69.40 ± 1.29 (66.87, 71.93)				75.13 ± 1.96 (71.29, 78.97)		
−2LogLikelihood, no. of parameters	3414.47, 10				4072.09, 11				1211.37, 8		

AFT = accelerated failure time; AUC = area under the curve; CC = clear cell; CI = confidence interval; df = degree of freedom; DFS = disease-free survival; EDP = early disease progression; IVC = inferior vena cava; OR = odds ratio; OS = overall survival; pap. = papillary; RCC = renal cell carcinoma; SE = standard error.

[a]In the absence of differentiable papillary histology, classify papillary into the same category as clear cell histology.