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Predicting Oncologic Outcomes in Renal Cell Carcinoma After Surgery

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Abstract

Background: Predicting oncologic outcomes is important for patient counseling, clinical trial design, and biomarker study testing.
Objective: To develop prognostic models for progression-free (PFS) and cancer-specific survival (CSS) in patients with clear cell renal cell carcinoma (ccRCC), papillary RCC (papRCC), and chromophobe RCC (chrRCC).
Design, setting, and participants: Retrospective cohort review of the Mayo Clinic Nephrectomy registry from 1980 to 2010, for patients with nonmetastatic ccRCC, papRCC, and chrRCC.
Intervention: Partial or radical nephrectomy.
Outcome measurements and statistical analysis: PFS and CSS from date of surgery. Multivariable Cox proportional hazards regression was used to develop parsimonious models based on clinicopathologic features to predict oncologic outcomes and were evaluated with c-indexes. Models were converted into risk scores/groupings and used to predict PFS and CSS rates after accounting for competing risks.
Results and limitations: A total of 3633 patients were identified, of whom 2726 (75%) had ccRCC, 607 (17%) had papRCC, and 222 (6%) had chrRCC. Models were generated for each histologic subtype and a risk score/grouping was developed for each subtype and outcome (PFS/CSS). For PFS, the c-indexes were 0.83, 0.77, and 0.78 for ccRCC, papRCC, and chrRCC, respectively. For CSS, c-indexes were 0.86 and 0.83 for ccRCC and papRCC. Due to only 22 deaths from RCC, we did not assess a multivariable model for chrRCC. Limitations include the single institution study, lack of external validation, and its retrospective nature.
Conclusions: Using a large institutional experience, we generated specific prognostic models for oncologic outcomes in ccRCC, papRCC, and chrRCC that rely on features previously shown—and validated—to be associated with survival. These updated models should inform patient prognosis, biomarker design, and clinical trial enrollment.
Patient summary: We identified routinely available clinical and pathologic features that can accurately predict progression and death from renal cell carcinoma following surgery. These updated models should inform patient prognosis, biomarker design, and clinical trial enrollment.

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1. Introduction

Renal cell carcinoma (RCC) represents a common urologic malignancy, with almost 64 000 cases and 14 400 deaths expected in 2017 [1]. While there is a strong association between pathologic stage and the risk of death [2], stage alone is insufficient to inform prognosis for most patients. Indeed, it has been shown that beyond American Joint Committee on Cancer (AJCC) stage other important factors to consider include manner of presentation, histology, grade, and associated findings such as the presence of histologic tumor necrosis or sarcomatoid features [3–5]. This variability in the behavior of RCC suggests the need for better methods to guide prognostication following surgery.

To this end, there have been numerous preoperative and postoperative nomograms designed for different outcomes in RCC [4–10]. Unfortunately, there are limitations with this myriad of models for risk prediction. Perhaps the most significant limitations have been the use of AJCC staging as a predictor of outcome and the failure to consider primary histology. While staging of RCC has been relatively constant, over the lifetime of the AJCC staging manual there have been subtle changes—such as the subdivision of cT1 into cT1a and cT1b with the advent of the seventh edition [11]—in the staging of RCC, which raises questions about the long-term applicability of models based on a given AJCC staging edition. Furthermore, while some models have been validated, their clinical utility has been limited by a dearth of functional tools for application in routine practice. Lastly, and most importantly, risk models to date have largely focused on clear cell RCC (ccRCC), neglecting the significant subset of patients with nonclear cell histologies [12]. Therefore, we sought to generate prognostic models for progression and death from RCC, accounting for all major histologic subtypes, and to operationalize these models into an easy-to-use clinical application.

2. Materials and methods

After obtaining Institutional Review Board approval, the Mayo Clinic Nephrectomy Registry was queried to identify binephric patients treated with radical or partial nephrectomy between 1980 and 2010 for sporadic, unilateral, nonmetastatic RCC. Clinical features abstracted included age at surgery, year of surgery, sex, race, presence of symptoms at diagnosis, smoking status, body mass index, Eastern Cooperative Oncology Group performance status, Charlson comorbidity score, preoperative estimated glomerular filtration rate, preoperative hemoglobin, and surgical details (approach, adjacent organ resection, lymph node dissection status). The presence of symptoms was defined as a palpable mass, pain, gross hematuria, acute onset varicocele, or the presence of constitutional complains, as has been previously defined and shown to be associated with outcome [4,5]. As over 20% of patients were missing data on liver function, serum calcium level, and platelet counts, these features were not included in analysis. Pathologic features, as rereviewed by one genitourinary pathologist (JCC), included surgical margin status, histologic subtype, 2016 World Health Organization/International Society of Urological Pathology grade [3,13], presence of coagulative necrosis, sarcomatoid differentiation, rhabdoid differentiation, tumor size, perinephric or renal sinus fat invasion, tumor thrombus presence/level, extension beyond Gerota's fascia, and lymph node status. For papillary RCC (papRCC), grade was used as a surrogate for subtype (eg, type I versus II) as has been previously shown [14]. All features were summarized with median and interquartile ranges (IQR) or frequencies and percentages, as appropriate.

The primary outcomes assessed were disease progression and death from RCC. Progression was defined as local ipsilateral recurrence, contralateral recurrence, or distant metastasis, while death from RCC was defined based on death certificate review or death following a recent medical visit for metastatic RCC. Follow-up assessment in the Mayo Clinic Nephrectomy Registry has been previously described [15]. The observed progression-free (PFS) and cancer-specific (CSS) survival rates were obtained using the Kaplan-Meier method, with follow-up calculated from date of surgery to date of outcome (progression or death from RCC) or last follow-up. Associations between clinicopathologic features and time to progression and time to death from RCC were evaluated using Cox proportional hazards regression models and summarized with hazard ratios and 95% confidence intervals (CIs). Where nonlinear associations were observed (eg, hemoglobin and tumor size), categorization was performed. In particular, hemoglobin levels were categorized into quartiles, and tumor size was divided into <4 cm, >4 cm to <7 cm, >7 cm to <10 cm, and >10 cm as per the 2010 AJCC pT classification [11]. Tumor thrombus level was defined by the Neves and Zinke levels [16], and was analyzed as none versus level 0 versus level I–IV after observing no additional association with level of thrombus beyond the renal vein and PFS or CSS.

Multivariable Cox proportional hazards regression models were developed using a 500-sample bootstrap resampling approach with forward and backward (ccRCC only) selection with the p value threshold for a feature to enter or leave a model set to 0.1. Features that were retained in 70% or more of the 500 samples were included in the final models. All models included year of surgery to account for changes in clinicopathologic features over time. Additionally, as opposed to the AJCC staging, where the highest stage item (such as renal vein involvement) supersedes all other staging components (such as size), all components included in staging were evaluated during model development. Predictive ability was summarized using bootstrap-corrected c-indexes, and p values for comparisons between two c-indexes were obtained using a jackknife approach. The predicted PFS and CSS rates at 5 yr, 10 yr, and 15 yr were obtained using the previously defined Cox proportional regression models and Fine and Gray proportional subdistribution hazard models accounting for the competing risk of death without progression or death from non-RCC causes [17]. All analyses were performed using SAS version 9.4 (SAS Institute; Cary, NC, USA) and R version 3.1.1 (R Foundation for Statistical Computing; Vienna, Austria), and all p values reported were two-sided.

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