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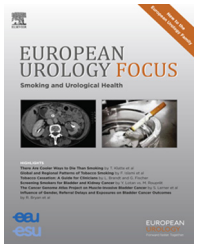

Kidney Cancer

Validation of a Postoperative Nomogram Predicting Recurrence in Patients with Conventional Clear Cell Renal Cell Carcinoma

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Abstract

Background: Clear cell renal cell carcinoma (RCC) continues to be the most commonly diagnosed subtype and is associated with more aggressive behavior than papillary and chromophobe RCC. Predicting disease recurrence after surgical extirpation is important for counseling and targeting those at high risk for adjuvant therapy clinical trials.
Objective: To validate a postoperative nomogram predicting 5-yr recurrence-free probability (RFP) for clinically localized clear cell RCC.
Design, setting, and participants: We identified all patients who underwent nephrectomy for clinically localized clear cell RCC from 1990 to 2009 at Memorial Sloan Kettering Cancer Center. After excluding patients with bilateral renal masses, familial RCC syndromes, and T3c or T4 tumors due to the limited number, 1642 participants were available for analysis.
Interventions: Partial or radical nephrectomy.
Outcome measurements and statistical analysis: Disease recurrence was defined as any new tumor after nephrectomy or kidney cancer–specific mortality, whichever occurred first. A postoperative nomogram was used to calculate the predicted 5-yr RFP, and these values were compared with the actual 5-yr RFP. Nomogram performance was evaluated by concordance index and calibration plot.
Results and limitations: Median follow-up was 39 mo (interquartile range: 14–79 mo), and disease recurrence was observed in 50 patients. The nomogram concordance index was 0.81. The calibration curve showed that the nomogram underestimated the actual 5-yr RFP. We updated the nomogram by including the entire patient population, which maintained performance and significantly improved calibration.
Conclusions: The updated clear cell RCC postoperative nomogram performed well in the combined cohort. Underestimation of actual 5-yr RFP by the original nomogram may be due to increased surgeon experience and other unknown variables.
Patient summary: We updated a valuable prediction tool used for assessing the disease recurrence probability after nephrectomy for clear cell renal cell carcinoma.

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1. Introduction

Kidney cancer continues to be one of the most commonly diagnosed genitourinary malignancies in Europe [1] and the United States [2]. Historically, 20–40% of patients experience disease recurrence after nephrectomy for clinically localized renal cell carcinoma (RCC) [3]. However, an analysis from the National Cancer Data Base shows a significant trend toward diagnosing RCC at earlier stages [4]. This stage migration, driven mainly by the increased use of abdominal imaging for nonspecific abdominal or musculoskeletal indications, has created new opportunities for surgical cure of tumors with aggressive biology. Nonetheless, the behavior of these cancers is heterogeneous, prompting analysis of clinicopathologic factors that can help counsel patients regarding their prognosis and target those at high risk of recurrence for adjuvant therapy clinical trials that may include targeted agents and/or immunotherapy.

RCC is subdivided into several histologic subtypes [5,6]. Across multiple studies, conventional clear cell RCC was not only the most common subtype diagnosed, accounting for 60–90% of all RCCs [7], but it also showed more aggressive behavior including higher rates of recurrence, metastasis, and death when compared with papillary and chromophobe RCC [8–11]. For this reason, we focused our efforts on clear cell RCC and developed a postoperative nomogram based on a cohort of 701 patients that predicts recurrence at 5 yr following surgery [12]. In the present study, we performed validation of this nomogram by including a contemporary cohort of patients who underwent surgery for clear cell RCC at Memorial Sloan Kettering Cancer Center (MSKCC).

2. Materials and methods

2.1. Patient selection

Institutional review board approval was obtained, and we identified all patients who underwent partial or radical nephrectomy for clinically localized clear cell RCC between 1990 and 2009 from a prospectively maintained kidney cancer database at MSKCC. Following the criteria from our published postoperative nomogram, patients with bilateral renal masses and familial RCC syndromes such as von Hippel-Lindau disease were excluded from the analysis [12]. Due to limited numbers, patients with T3c and T4 tumors as well as those with sarcomatoid elements were also excluded from the analysis. The cohort that underwent analysis contained 1642 patients.

2.2. Disease characterization

Presurgical staging consisted of abdominopelvic cross-sectional imaging to characterize the kidney tumor and detect metastatic disease below the diaphragm as well as chest radiograph to rule out lung metastasis. If findings suspicious for metastatic disease were discovered on these studies and/or the patient reported symptoms suggestive of systemic disease, additional imaging such as computed tomography (CT) chest, CT brain, or bone scan were obtained to rule out metastatic disease prior to nephrectomy.

A group of experienced uropathologists determined the histologic features of the tumors that included subtype according to the Heidelberg classification [5], Fuhrman grade [13], presence of microvascular invasion, and tumor necrosis. Tumor staging was performed according to the American Joint Committee on Cancer Staging Manual, 6th ed., published in 2002 [14]. Clinical presentation was classified as incidental, locally symptomatic, or systemically symptomatic. Incidental lesions were defined as tumors detected on abdominal imaging for an unrelated condition. Local symptomatic lesions were defined as tumors that presented as an abdominal mass or were associated with ipsilateral flank pain or hematuria. Systemic symptomatic lesions were defined as tumors causing paraneoplastic signs and symptoms such as fever, night sweats, weight loss, extreme fatigue, anemia, hypercalcemia, and hepatic dysfunction.

2.3. Definition of recurrence

Patients were followed with chest radiograph and renal/retroperitoneal ultrasound or cross-sectional imaging every 3–6 mo, depending on pathologic stage and grade. In general, patients with greater than pathologic T2 disease or Fuhrman grade 3–4 underwent more intense follow-up. For patients who chose not to obtain follow-up studies at our institution, we reviewed outside imaging when available. Disease recurrence was defined as the appearance of any new tumor of RCC origin after nephrectomy or kidney cancer–specific mortality, whichever event occurred first. Patterns of disease recurrence included local, metastatic, or a metachronous tumor in the contralateral kidney, but this information was not used in the analysis.

2.4. Statistical analysis

Chi-square and Fisher exact tests were used to compare clinicopathologic data between the present cohort and the cohort from Sorbellini et al [12]. Using clinicopathologic data gathered from each patient, the conventional clear cell RCC postoperative nomogram [12] was used to calculate the 5-yr predicted recurrence-free probability (RFP). Model validation was conducted in two ways. First, the discrimination ability was evaluated with the Harrell concordance index (c-index) [15], which is equivalent to the area under the receiver operating characteristic curve but tailored to the censored outcomes. C-index values range from 0.5, indicating no discrimination ability, to 1.0, indicating perfect discrimination. Calibration accuracy was evaluated by plotting predicted versus actual 5-yr RFP. The 5-yr RFP was estimated using the Kaplan-Meier method. The Sorbellini cohort and present cohort were combined to generate an updated nomogram. Statistical analyses were performed using the open source R statistical software v.3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) with packages *utils, base, ClevClinicQHS, rms*, and *Hmisc*.

3. Results

Table 1 details the clinicopathologic characteristics of the patient cohort examined. A total of 1642 patients were available for analysis. One patient did not have information for presentation type and was excluded, so the final cohort consisted of 1641 patients. Overall, 829 (50%) underwent partial nephrectomy, and the remainder underwent radical nephrectomy. Most of the patients presented with a pT1a (49.8%) or pT1b (21.3%) tumor. The median tumor size was 3.9 cm (interquartile range [IQR]: 2.6–5.8 cm). A total of 195 (11.9%) of the patients had a Fuhrman grade I tumor, 913 (55.6%) had Fuhrman grade II, 427 (26.0%) had Fuhrman grade III, and 107 (6.5%) had Fuhrman grade IV. Necrosis was present in 122 patients

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