Risk Assessment in Small Renal Masses
A Review Article

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KEYWORDS

• Renal cell carcinoma • Prediction models • Prognostic models • Risk assessment • Nomograms • Oncologic outcomes • Small renal masses • Localized

KEY POINTS

- The incidence of localized renal cell carcinoma (RCC) has been steadily increasing, in large part because of the increased use of imaging.
- Optimizing the management of localized RCC has become one of the leading priorities and foremost challenges within the urologic-oncologic community.
- Adequate risk stratification of patients following the diagnosis of localized RCC has become meaningful in deciding whether to treat, how to treat, and how intensively to treat.

INTRODUCTION

Approximately 60% of patients with renal cell carcinoma (RCC) present with localized disease.[1] The incidence of RCC has been steadily increasing,[2] likely because of the increased use of imaging.[3] More patients are diagnosed with asymptomatic small renal masses (SRMs), of which most are early-stage RCC. Historically, patients with localized disease were predominantly treated with radical nephrectomy with curative intent. However, this strategy has not led to a decrease in mortality, calling into question the need to treat every SRM at first diagnosis. The lack of effect has been attributed to the sometimes indolent nature and clinical heterogeneity of SRMs.[4] Optimizing the management of localized RCC has become one of the leading priorities and foremost challenges within the urologic-oncologic community as clinicians struggle to identify who needs upfront surgery and who might be followed with close monitoring (ie, active surveillance).

At present, no biomarkers are known that can reliably and accurately differentiate between a benign SRM, a clinically indolent RCC, and an aggressive form of RCC.[5] Consequently, developing adequate risk stratification nomograms following the diagnosis of localized RCC has become very important. The primary step is for the patients and clinicians to make informed decisions on whether to surgically treat (ie, radical nephrectomy, partial nephrectomy) or nonsurgically treat (ie, active surveillance, tumor ablation). This decision needs to take into consideration the trade-offs between the oncologic benefits of surgery (ie, overall survival, cancer-specific mortality) and treatment-related morbidities (ie, chronic kidney disease, surgical complications, perioperative

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mortality). Second, in patients who are selected for surgery, consideration of nephron-sparing surgery remains essential. Furthermore, correctly classifying a patient's risk of recurrence has become especially important. Evidence shows that between 20% and 40% of patients recur within 3 years following a nephrectomy,[6] and that between 10% and 20% of patients recur beyond 5 years following a nephrectomy.[7] Such individuals, if correctly identified, can potentially benefit from adjuvant therapy.[8]

This article characterizes existing risk assessment models for prediction of outcomes in the preoperative and postoperative settings. Of note, it does not focus on individual risk factors, which are beyond the scope of the article, but focuses on models that include a variety of prognostic factors. Furthermore, because most of these studies developed their models based on patients with localized disease (nonmetastatic RCC) and not specifically patients with SRMs, this article includes the proportion of patients with T1a disease whenever reported in the original study.

PREOPERATIVE SETTING

Risk assessment models that were developed for patients with renal cell carcinoma used in the preoperative setting are described in (**Table 1**).

Predicting Malignant Versus Benign Disease

Incidentally detected SRMs (<4 cm) account for more than 40% of RCC diagnoses.[9] Between 20% and 30% of these lesions ultimately prove to be benign, instilling uncertainly into practitioners as to how aggressively to treat.[10,11] With the increased use of renal mass biopsy,[12] clinicians can more easily distinguish between malignant and more indolent histologies. In addition, some studies have highlighted the potential association between renal mass anatomy and pathology, but it clearly is not sensitive enough to form the basis of the surgical decision.[13–15] For example, Schachter and colleagues[14] reported that 13.5% of exophytic tumors were oncocytoma versus 9.2% of central tumors. Venkatesh and colleagues[15] also showed that 44.9% of exophytic tumors were benign compared with 15.8% of endophytic tumors.

For the purpose of better counseling patients with an enhancing renal mass, Kutikov and colleagues[16] developed a nomogram for prediction of malignant disease using the characteristics of tumor anatomy of 525 patients who underwent a nephrectomy at their institution. Most had early stage T1a disease (43%). The model incorporated gender, gender-stratified age, and components of the RENAL (radius, exophytic or endophytic properties, nearness of the tumor, anterior or posterior, location; discussed later) nephrometry score[17] (discussed further later). It encompasses radius, exophytic properties, proximity of the tumor to the collecting system or renal sinus, location relative to the polar lines, and hilar location. The model showed moderate predictive accuracy to identify malignant renal masses (centrality index [concordance index (c- index)] for the development cohort, 0.76; c-index for the cross-validation cohort, 0.68).

In a comparable study, a multicenter initiative focused on 1009 patients with clinically localized RCC (<4 cm) treated with partial nephrectomy at 5 single institutions between years 2007 and 2013.[18] Also relying on the RENAL nephrometry score, the investigators developed a model for prediction of malignant disease. In the final multivariable model, male sex, tumor diameter of greater than or equal to 3 cm, and a nephrometry score of greater than or equal to 8 points were significantly associated with malignancy (c-index, 0.62).

Predicting Unfavorable Pathology

At final pathology, only between 10% and 30% of lesions from SRMs are considered aggressive.[10] According to a population-based study of the Surveillance, Epidemiology, and End Results (SEER) database focusing on patients with less than or equal to 3 cm RCC between years 1988 and 2007 (n = 14,962), only 3% of patients had distant metastasis.[19]

Kutikov and colleagues,[16] in the same study that developed a nomogram for prediction of malignant disease, also developed a second nomogram for prediction of high-grade RCC. The retained variables in that model included sex and the nephrometry score (c-index for the development cohort, 0.73; c-index for the cross-validation cohort, 0.69). The ability of the RENAL nephrometry score to discriminate against patients with high-grade RCC was also externally validated in a Chinese population (n = 391) treated at a single institution between 2008 and 2011 (c-index, 0.73).[20] In their decision curve analysis, the investigators showed that the model provided a superior net benefit with a threshold probability of up to 20%. Ball and colleagues[18] also reported that male sex, tumor diameter of greater than or equal to 3 cm, and a nephrometry score of greater than or equal to 8 points were highly predictive of unfavorable pathology, defined as Fuhrman grade III to IV or lesions upstaged to pathologic T3a on surgery (c-index, 0.63).

Other studies have attempted to predict the risk of harboring nodal metastases. For example, Hutterer and colleagues[21] relied on data from 2522