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The Probability of Aggressive Versus Indolent Histology Based on Renal Tumor Size: Implications for Surveillance and Treatment

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Abstract

Background: While the probability of malignant versus benign histology based on renal tumor size has been described, this alone does not sufficiently inform decision-making in the modern era since indolent malignant tumors can be managed with active surveillance.
Objective: To characterize the probability of aggressive versus indolent histology based on radiographic tumor size.
Design, setting, and participants: We evaluated patients who underwent radical or partial nephrectomy at Mayo Clinic for a pT1-2, pNx/0, M0 solid renal tumor between 1990 and 2010. Pathology was reviewed by one genitourinary pathologist. High-grade clear-cell renal cell carcinoma (RCC), high-grade papillary RCC, collecting duct RCC, translocation-associated RCC, hereditary leiomyomatosis RCC, unclassified RCC, and malignant non-RCC tumors were all considered aggressive, as well as any tumors demonstrating coagulative necrosis (except low-grade papillary RCC) or sarcomatoid differentiation. The remaining benign and malignant tumors were considered indolent.
Outcome measurements and statistical analysis: Cancer-specific survival (CSS) was estimated using the Kaplan-Meier method. Logistic regression models were used to estimate the probability of malignant and aggressive histology based on tumor size. Sex-stratified analyses were also performed.
Results and limitations: Of the 2650 patients included, there were 1860 patients with indolent tumors (300 benign; 1560 malignant) and 790 with aggressive tumors. The 10-yr CSS was 96% for indolent malignant tumors and 81% for aggressive malignant tumors. The predicted percentages of any malignant histology as well as aggressive histology increased with tumor size. Specifically, 2 cm, 3 cm, and 4 cm tumors have an estimated 84%, 87%, and 88% likelihood of malignancy, respectively, and an 18%, 24%, and 29% likelihood of aggressive histology, respectively. For any given tumor size, men had a greater chance of aggressive histology than women. Potential limitations of this observational surgical cohort include selection bias.
Conclusions: We present tumor size-based estimates of the probability of aggressive histology for renal masses. This information should be useful for initial patient counseling and management.
Patient summary: Active surveillance is an option for kidney masses, even if they are malignant. Beyond knowing whether the mass is benign or cancer, it is important to know whether or not it is an aggressive tumor. This study presents tumor size-specific and sex-specific estimates of the probability of cancer overall and aggressive cancer among patients with a kidney mass in order to aid with initial decision-making.

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1. Introduction

The decision whether to offer active surveillance, surgical resection, or percutaneous ablation to patients with renal tumors is often made without a histologic diagnosis [1]. Given that the most common presentation is an asymptomatic incidental renal mass [2], radiographic tumor features, including tumor size, are an important part of the clinical assessment.

Increasing tumor size has been shown to be associated with increasing risk of malignant histology [3–15]. However, knowledge of malignant versus benign histology is not sufficiently informative on its own in the modern era. It has been shown in active surveillance series that many small renal masses follow an indolent course, even though 70–80% of them are malignant [16–19]. Although imaging characteristics [20] along with renal mass biopsy [21–23] can be used to discern malignant versus benign histology, to date, these approaches are limited in their ability to reliably distinguish aggressive versus indolent disease [20,22].

For a given patient, the decision between active surveillance and active treatment usually depends on an individualized weighting of cancer mortality risk, the radiographic characteristics of the tumor, and comorbidity-related mortality risk. In this regard, knowledge of the probability of harboring an aggressive tumor would better inform estimation of a patient's oncologic risk. As such, our objective was to characterize the probability of aggressive versus indolent histology based on radiographic tumor size.

Table 1 – Histologic classification

Indolent [a]	Aggressive [a]
Benign and indolent	Aggressive clear-cell RCC [c]
Oncocytoma	Aggressive papillary RCC [c]
Non-epithelioid angiomyolipoma [b]	Collecting duct RCC
Papillary adenoma	Unclassified RCC
Metanephric adenoma	Translocation-associated RCC [27]
Other benign tumors	Hereditary leiomyomatosis RCC [28]
	Other malignant non-RCC tumors
Malignant and indolent	
Epithelioid angiomyolipoma [b]	
Indolent clear-cell RCC [c]	
Indolent papillary RCC [c]	
Chromophobe RCC [d]	
Clear-cell papillary RCC [28,30]	
Tubulocystic RCC [32]	
Mucinous tubular and spindle cell RCC [31]	
Succinyl dehydrogenase deficient RCC [28]	

RCC = renal cell carcinoma.
[a] The presence of any sarcomatoid differentiation led to the classification of malignancies as aggressive. The presence of coagulative necrosis also led to the classification of malignancies as aggressive, except for low-grade (1–2) papillary RCC, where it does not appear to portend a poor prognosis [26].
[b] Epithelioid angiomyolipoma was considered malignant given its ability to metastasize, but indolent in behavior [33,34].
[c] In addition to sarcomatoid differentiation (both clear-cell and papillary RCC) and necrosis (clear-cell RCC), any high-grade (3–4) component led to aggressive classification for clear-cell and papillary RCC.
[d] Chromophobe RCC was not graded as per International Society of Urological Pathology 2012 Consensus Recommendations [29] and was considered indolent if sarcomatoid differentiation and coagulative necrosis were absent.

2. Materials and methods

2.1. Study participants

Following institutional review board approval, the prospectively-maintained Mayo Clinic Nephrectomy Registry was queried to identify 2650 patients treated with radical or partial nephrectomy for a sporadic, unilateral, pT1/2, pNX/0, M0 solid renal tumor between 1990 and 2010. All pathology was reviewed by one experienced genitourinary pathologist (J.C.C.).

2.2. Exposure and outcomes

The primary exposure was radiographic tumor size, measured as the largest tumor dimension on cross-sectional imaging. Linear size was used instead of volumetric size so that our findings would be more readily generalizable to the clinical setting.

The primary outcome was the presence of aggressive versus indolent histology (Table 1) [24]. Any sarcomatoid differentiation was defined as aggressive histology [25]. Coagulative necrosis was also considered as aggressive histology, except for low-grade (International Society of Urological Pathology grade 1–2) papillary renal cell carcinoma (RCC) [26]. Aggressive tumors included high-grade clear-cell RCC, high-grade papillary RCC, collecting duct RCC, translocation-associated RCC [27], hereditary leiomyomatosis RCC [28], unclassified RCC, and other malignant non-RCC tumors. Meanwhile, along with benign tumors, malignant tumors considered indolent included low-grade clear-cell and papillary RCC, chromophobe RCC [29], and clear-cell papillary [28,30], mucinous tubular and spindle cell [31], succinyl dehydrogenase deficient [28], and tubulocystic RCC [32] of any grade. Epithelioid angiomyolipoma was considered malignant given its metastatic potential but was considered indolent given its available outcome data to date [33,34]. The presence of malignant versus benign histology was evaluated as a secondary outcome.

Survival outcomes included progression-free (PFS) and cancer-specific survival (CSS) from the date of surgery, with disease progression defined as local ipsilateral recurrence, distant metastases, or death from RCC [35].

2.3. Statistical analyses

Clinical and pathologic features were summarized with medians and interquartile ranges (IQRs) or frequency counts and percentages, and compared between patients with benign and malignant and between patients with indolent and aggressive histology using Wilcoxon rank sum and Fisher exact tests. The percentages of patients with benign, malignant, indolent, and aggressive histology were tabulated per 1 cm increments of radiographic tumor size. The impact of tumor size on malignant histology and grade were similarly evaluated using Kruskal-Wallis and

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