Renal Mass Biopsy to Guide Treatment Decisions for Small Incidental Renal Tumors: A Cost-effectiveness Analysis

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Purpose: To evaluate the effectiveness, cost, and cost-effectiveness of using renal mass biopsy to guide treatment decisions for small incidentally detected renal tumors.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for more than 80% of cancers of the kidney and renal pelvis, which were predicted to have resulted in over 12 980 deaths and 57 760 new cancer diagnoses in the United States in 2009 (1–3).

A continual rise in RCC incidence is attributed largely to increased detection, with more than 60% of RCCs discovered incidentally at imaging (4).

Small (≤4-cm) RCCs account for the majority of increased detection and carry a favorable prognosis (5,6). However, despite increased detection and surgery, RCC mortality has not decreased, suggesting tumor indolence (5). These trends underscore the need to reassess renal tumor management paradigms, particularly the effects of less aggressive strategies on patient outcomes.

The use of renal mass biopsy to guide subsequent management decisions has the potential to reduce the number of patients who receive unnecessary surgery for small tumors. However, the appropriate use of renal mass biopsy is controversial. Proponents of biopsy argue that a substantial proportion of detected lesions are benign and that biopsy can therefore help avoid unnecessary treatment in many patients (7–10). Those who oppose biopsy cite two primary potential disadvantages: a high reported false-negative rate for RCC detection (11) and a risk of biopsy track seeding with cancer cells (12,13).

Empiric surgery without pretreatment biopsy is the standard of care in many major centers. However, advances in specimen procurement and analysis have improved biopsy accuracy (14).

Moreover, newer minimally invasive tumor treatments, such as radiofrequency ablation and cryoablation, necessitate preprocedure biopsy for histology-based prognostication (9,15).

These factors, combined with increased awareness of the indolent natural history of most small incidentally detected renal tumors, have forced practitioners to reconsider the role of renal mass biopsy (9,10,14).

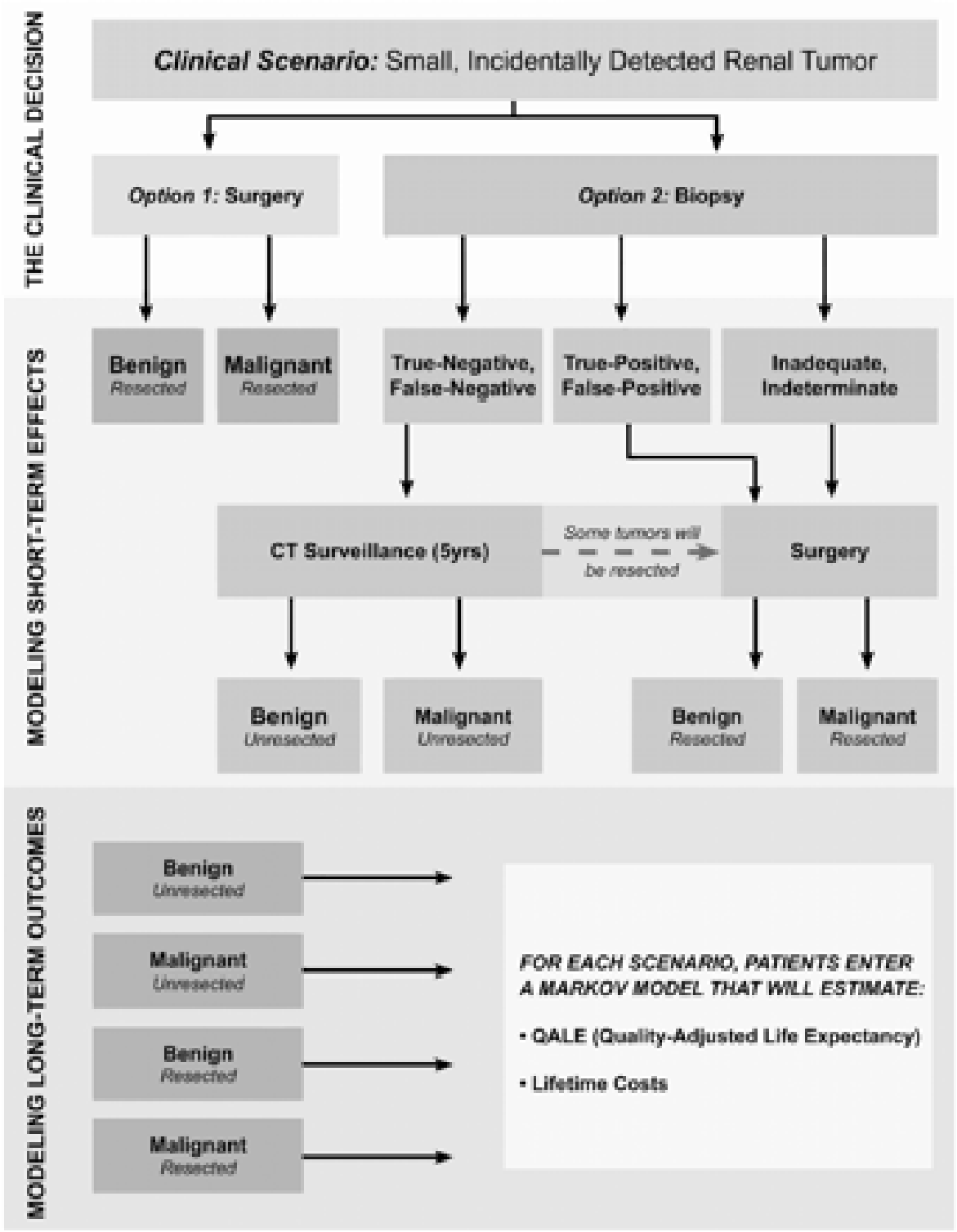
Before biopsy can be routinely advocated for small incidentally detected renal tumors, its risks, benefits, and long-term consequences must be carefully evaluated and compared with those of empiric surgery. To perform a definitive comparison, a large randomized clinical trial would be necessary. A large number of patients would be required to enable detection of small differences in outcomes, as would a long follow-up period, given the high proportion of these tumors that are benign or indolent. The resources required to conduct such a trial would be prohibitive.

Decision analysis provides an ideal method for comparing management paradigms for incidentally detected renal tumors, enabling efficient incorporation of the relative risks and benefits of each strategy considered and of numerous other factors that influence long-term outcomes. In this study, we developed a decision-analytic model to evaluate renal mass biopsy versus empiric surgery for the initial management of small incidentally detected renal tumors and compared the life expectancy, lifetime health care costs, and relative cost-effectiveness of each approach.

Materials and methods

Cost-effectiveness Analysis Overview

We used cost-effectiveness analysis to compare two management strategies for small solid incidentally detected renal masses: *(a)* biopsy to guide the decision to operate and *(b)* direct nephron-sparing surgery (NSS) without preceding biopsy, which we refer to as empiric NSS.


THE CLINICAL DECISION
Clinical Scenario: Small, Incidentally Detected Renal Tumor
Option 1: Surgery
Option 2: Biopsy
MODELING SHORT-TERM EFFECTS
Benign
Resected
Malignant
Resected
True-Negative,
False-Negative
True-Positive,
False-Positive
Inadequate,
Indeterminate
CT Surveillance (5yrs)
Some tumors will
be resected
Surgery
Benign
Unresected
Malignant
Unresected
Benign
Resected
Malignant
Resected
MODELING LONG-TERM OUTCOMES
Benign
Unresected
Malignant
Unresected
Benign
Resected
Malignant
Resected
FOR EACH SCENARIO, PATIENTS ENTER
A MARKOV MODEL THAT WILL ESTIMATE:
• QALE (Quality-Adjusted Life Expectancy)
• Lifetime Costs

Parameter and Source	BCE	Sensitivity Analysis Range
Patient age (y) (25)	65	45–85
Patient sex	Male	Female
Biopsy sensitivity (11,14,26–30)	0.90	0.5–1.0
Biopsy specificity (14,27,31–36)	1.0	0.5–1.0
Probability of nondiagnostic biopsy (14)*	0.088 (32/362)	(0.5–1.5) × BCE
Probability of biopsy complication (14)	0.047 (17/362)	0–0.1
Probability of biopsy track seeding with malignant cells (12)	0.00006 (1/16 381)	0–0.001
NSS mortality rate (37)	0.016 (14/899)	0–0.1
Prevalence of malignancy (RCC) in ≤4-cm tumors (7)	0.77 (726/947)	0–1.0
Yearly probability of tumor growth during CT surveillance of biopsy-negative tumors (38–43)†	0.38	(0.5–1.5) × BCE
Proportion of growing biopsy-negative tumors resected at each surveillance point (38–45)‡	0.29	0–1.0
Yearly probability of development of metastasis from unresected biopsy-negative RCC (38–45)‡	0.012	(0.5–1.5) × BCE
Yearly probability of postoperative local recurrence of RCC (46–51)‡	0.0031	(0.5–1.5) × BCE
Yearly probability of development of metastases after NSS (46–51)‡	0.0044	(0.5–1.5) × BCE
Yearly probability of development of metastases after local recurrence (52,53)§	0.20	(0.5–1.5) × BCE
Yearly probability of death due to metastatic RCC (52)§	0.35	(0.5–1.5) × BCE
Yearly age-specific probability of death from unrelated causes (54)	U.S. Life Tables	(0.5–1.5) × BCE

Parameter and Source	BCE ($)*	Sensitivity Analysis Range
Cost of renal mass biopsy (55)	825	(0.5 × BCE) to threshold†
Cost of renal mass biopsy with complications (55)	1141	(0.5 × BCE) to threshold†
Short-term cost of NSS and ≤1-month follow-up (56)	32 027	Threshold to (1.5 × BCE)†
Cost of surveillance CT‡	478	(0.5–1.5) × BCE
Baseline yearly costs without renal tumor–related events (57)	Age-specific medical expenditures	(0.5–1.5) × BCE
Initial cost of local RCC recurrence§	32 027	(0.5–1.5) × BCE
Yearly cost of metastatic RCC (58)‖	8554	(0.5–1.5) × BCE
Patient utilities (for quality-adjustment of life-years) (59)	Age/sex-specific utilities (community-elicited)	(0.5 × BCE)–1
Discount rate (16)#	3%	0%–5%

First Author	Tumors*	Mean Size (cm)	Mean Follow-up (mo)	Pathologic Correlation (%)	Malignant Tumors (%)	Metastasis during Observation	Tumors that Grew during Follow-up (%)
Crispen (40)	173	2.5	31	38 (66/173)	86 (57/66)	2	74 (128/173)
Kouba (41)	46	2.9	36	30 (14/46)	86 (12/14)	0	74 (34/46)
Bosniak (39)	40	1.7	39	65 (26/40)	85 (22/26)	0	95 (38/40)
Volpe (42)	32	2.5	35	28 (9/32)	89 (8/9)	0	88 (28/32)
Wehle (43)	29	1.8	32	17 (5/29)	80 (4/5)	0	48 (14/29)
Sowery (45)	22	4.1	26	9 (2/22)	100 (2/2)	1	…†
Abou Youssif (44)	44	2.2	48	20 (9/44)	78 (7/9)	2	…†
Abouassaly (38)	89‡	2.5§	24§	9 (8/89)	38 (3/8)	0	57 (51/89)
Summary statistics	475	2.5‖	33‖	29 (139/475)	83 (115/139)	1% (5/475)	72 (293/409)

Importantly, the data that we used to inform biopsy performance in our model were derived predominantly from studies that reported use of 18-gauge or larger needles or a combination of core biopsy and fine needle aspiration (14,26–29,31–35,60), but a few studies used fine needle aspiration only (11,30). Practice patterns in using core biopsy and fine needle aspiration for renal tumor sampling differ by institution. Our model is not prescriptive about how biopsy performance is achieved. Instead, it provides predictions based on explicit assumptions of test performance that we outline in this section.

Patients with true- or false-negative biopsy results underwent CT surveillance for 5 years (every 6 months for 2 years and then yearly), as is a common approach at our institution. There is no universally accepted surveillance strategy in this setting. Further complicating the practice of CT surveillance is that no significant difference in tumor growth has been demonstrated between benign and malignant tumors, although this could be related to the overall low number of reported tumors that have been managed with imaging surveillance to date (61). Currently, fast-growing tumors are resected, and tumors with zero or minimal growth are often managed without surgery.

We assumed a sensitivity of 90% for RCC detection with biopsy. The reported sensitivity of renal mass biopsy for diagnosing malignant tumors ranges from 76% (19 of 25) (11) to 100% (31 of 31) (26), with several published reports substantiating this range (11,14,26–30). Within this range, there is a trend toward 100% or near-perfect sensitivity values in more recent years, attributable in part to improved technique and advances in tissue characterization (9,10,14). However, because practitioners have become more confident in renal mass biopsy results, fewer correlative surgical histologic results for biopsy-negative tumors are available (9,10,14,26,29,62), and the use of tumor indolence as a proxy for surgical confirmation of benignity has increased. However, clinical follow-up of false-negative results does not prove tumor benignity, and the assumption that tumor indolence and benignity are equivalent may contribute to higher reported sensitivity values in recent years. Incorporating these considerations, we used a conservative estimate of 90% in our base-case analysis, but varied this value substantially in sensitivity analysis (Table 1).

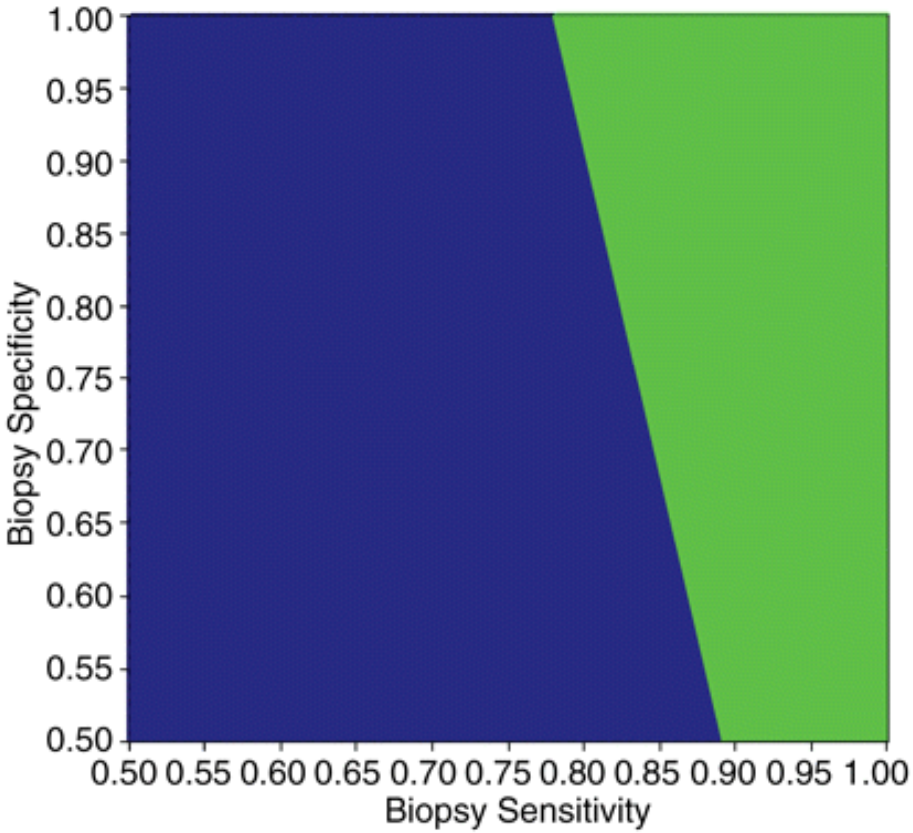
We assumed a specificity of 100% for renal mass biopsy. In a systematic review, Lane et al (14) found no false-positive results in seven series reported since 2001, with a total of 172 pathologically confirmed lesions (27,31–36). False-positive pathologic results that have been reported in the literature (eg, misdiagnosis of an angiomyolipoma [63] or a multilocular cystic nephroma [64] as a malignancy) were predominantly reported more than 2 decades ago (9). A lack of recent reports is thought to be owing to interval advances in specimen procurement and characterization (9). While the rarity of false-positive results is widely recognized (9,14), we also varied our estimate of 100% widely in sensitivity analysis to determine potential effects on our analysis results (Table 1).

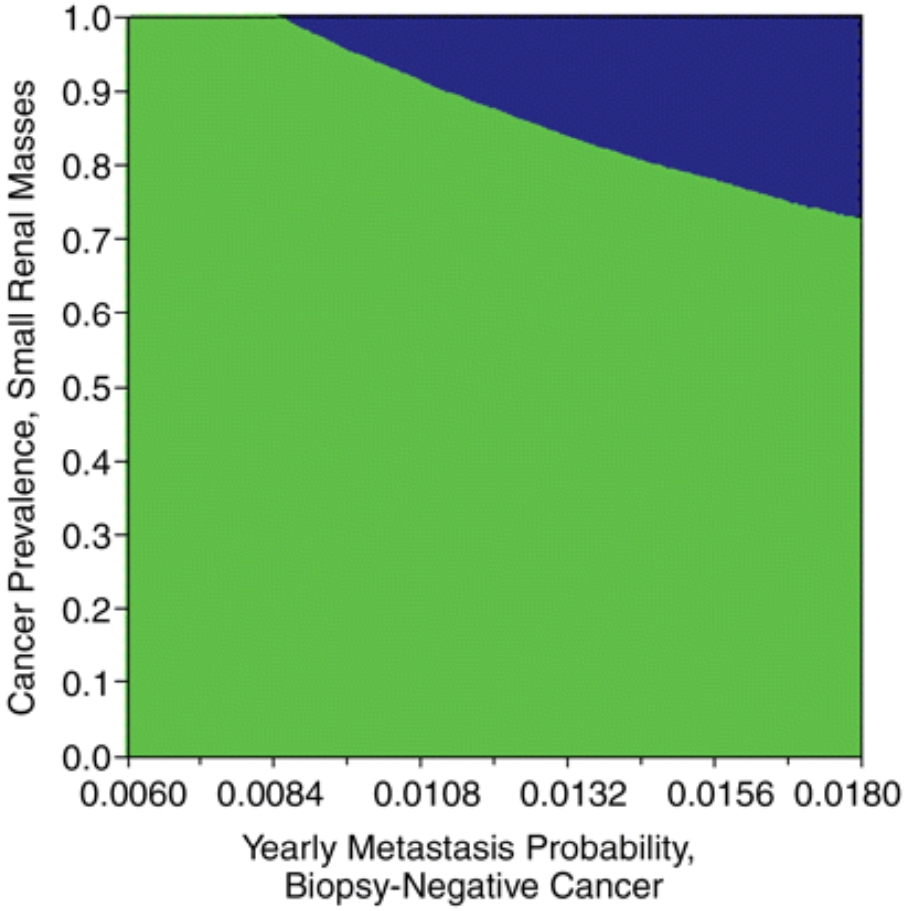
We accounted for complications of renal mass biopsy in our analysis by including a cost penalty for patients who incurred complications. Lane et al (14) found an overall complication rate of 4.7% (17 of 362), a major complication rate of 0.3% (one of 362), and no mortalities consequent to renal mass biopsy. We applied a uniformly increased cost to biopsies associated with any complications on the basis of reported costs attributable to complications from abdominal biopsies (see Appendix [online] for details) (55). We widely varied our cost estimate for a biopsy with associated complications in sensitivity analysis to determine the potential effects on our analysis results.

results

Strategy	QALE (y)*	Lifetime Cost ($)*
Biopsy	9.651	206 242
Empiric NSS	9.640	209 709
Difference	−0.011†	+3466

Parameter	BCE	Sensitivity Range Tested	Threshold	
			Biopsy No Longer Dominant vs Empiric NSS	Biopsy No Longer Cost-effective vs NSS*
Prevalence of malignancy (RCC) in ≤4-cm tumors	0.77†	0–1	>0.87	>0.98
Yearly probability of development of metastasis from unresected biopsy-negative RCC	0.012‡	0.006–0.018	>0.016	DNE§
NSS mortality rate	0.016‖	0–0.1	<0.01	DNE§
Biopsy sensitivity	0.9#	0.5–1	<0.78	DNE§
Cost of renal mass biopsy ($)	825	412 to threshold**	>4291	>5141
Cost of renal mass biopsy with complications ($)	1141	570 to threshold**	>74 943	>93 021
Short-term cost of NSS and ≤1-month follow-up ($)	32 027	Threshold to 48 040**	<11 895	<6963


1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
Biopsy Specificity
0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00
Biopsy Sensitivity


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Cancer Prevalence, Small Renal Masses
0.0060
0.0084
0.0108
0.0132
0.0156
0.0180
Yearly Metastasis Probability,
Biopsy-Negative Cancer

Discussion:

The role of renal mass biopsy in managing renal tumors has been controversial, primarily owing to two biopsy risks: the potential for false-negative results and the possibility of biopsy track seeding with cancer cells (11–13). We nonetheless found that use of biopsy to triage patients to surgery yielded a life expectancy comparable to that with an empiric surgical approach and, thus, could safely prevent many patients from undergoing unnecessary surgery.

Put another way, the risks that have historically precluded practitioners from using biopsy for renal tumor management are at least equaled by those risks incurred by performing empiric surgery in all patients. We also found that the biopsy approach resulted in cost savings. Our results support the use of biopsy to manage small incidentally detected renal tumors.

Importantly, the primary factor driving our results was not the accuracy of biopsy, but instead the indolent behavior of most small renal tumors. In the biopsy strategy, most RCCs are resected initially, without triage to imaging surveillance, because of the high sensitivity of biopsy for RCC. However, we found that, even if the accuracy of biopsy were to be substantially lower, the resulting effect on life expectancy would be minimal. This is because of the relatively low propensity for patients with small unresected RCC to develop metastases during surveillance (38–45,67). From a life-expectancy perspective, the small risk of incorrectly triaging a biopsy-negative RCC to imaging surveillance is unlikely to exceed the risks of empiric NSS.

The potential for biopsy track seeding with malignant cells (<0.01% [12]) is frequently cited as a reason to avoid renal mass biopsy. In our analysis, we incorporated a worst-case scenario for each instance of biopsy track seeding and assumed that it was equivalent to the development of metastatic disease. Under this assumption, even when the probability of track seeding was increased to 0.1%, the biopsy strategy continued to yield a minimally higher life expectancy compared with empiric surgery at a lower expense. Because urothelial malignancies can have a higher potential to seed track sites than RCC, if there is strong suspicion of urothelial malignancy (ie, central location, close association with collecting system, ill-definition), a ureteroscopic approach to tissue sampling may be more prudent. However, the majority of small, solid, well-defined renal masses are RCC if they are malignant and, on the basis of our analysis of risks and benefits, are safe to biopsy.

In previous work, we found that radiofrequency ablation is likely to be cost-effective relative to NSS for small proved RCC (17). Ultimately, future cost-effectiveness research relevant to ablative techniques should aim to quantitatively evaluate and compare the effectiveness, costs, and cost-effectiveness of all possible treatment strategies for small renal tumors, including NSS with and without preprocedural biopsy, radiofrequency ablation and cryoablation with and without preprocedural biopsy, and watchful waiting. The insights gained from such an analysis could inform the design of future clinical trials related to the use of minimally invasive therapies for renal tumors and set future research priorities by identifying those model parameters that drive the analysis results but that have been inadequately studied to date.

In conclusion, renal mass biopsy is a cost-effective approach for managing small incidentally detected renal tumors. Use of biopsy to triage patients to surgery will, on average, result in comparable life expectancy relative to empiric surgery at a lower cost and safely prevent unnecessary surgery in many patients.

Our results are consistent with emerging recommendations that support an increased role for biopsy in managing small renal tumors, particularly for patients who have reduced life expectancy or multiple comorbid conditions (9,10).

Practitioners are encouraged to discuss the option of biopsy with patients who have small incidentally detected renal tumors, outlining risks and benefits of biopsy versus empiric surgery for each individual patient. Importantly, our predictions of cost and effectiveness address the average patient encounter.
Tumor position and the requisite biopsy approach are primary examples of factors that can change the risks and likelihood of adverse outcomes when performing a biopsy—such risks must be weighed for each individual patient.

Finally, further studies that detail the natural history of renal tumors in larger populations will be critical to more precisely estimate the course of patients with biopsy-negative RCC. Such studies also will allow us to better validate our model predictions and to more broadly understand how surveillance strategies can be optimized for managing biopsy-negative tumors.