Renal Mass Biopsy to Guide Treatment Decisions for Small Incidental Renal Tumors:

A Cost-effectiveness Analysis¹

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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.

Materials and Methods:

A decision-analytic Markov model was developed to estimate life expectancy and lifetime costs for patients with small (≤ 4 -cm) renal tumors. Two strategies were compared: renal mass biopsy to triage patients to surgery or imaging surveillance and empiric nephron-sparing surgery. The model incorporated biopsy performance, the probability of track seeding with malignant cells, the prevalence and growth of benign and malignant tumors, treatment effectiveness and costs, and patient outcomes. An incremental cost-effectiveness analysis was performed to identify strategy preference under a willingness-to-pay threshold of \$75 000 per quality-adjusted life-year (QALY). Effects of changes in key parameters on strategy preference were evaluated in sensitivity analysis.

Results:

Under base-case assumptions, the biopsy strategy yielded a minimally greater quality-adjusted life expectancy (4 days) than did empiric surgery at a lower lifetime cost (\$3466), dominating surgery from a cost-effectiveness perspective. Over the majority of parameter ranges tested in one-way sensitivity analysis, the biopsy strategy dominated surgery or was cost-effective relative to surgery based on a \$75 000-per-QALY willingness-to-pay threshold. In two-way sensitivity analysis, surgery yielded greater life expectancy when the prevalence of malignancy and propensity for biopsy-negative cancers to metastasize were both higher than expected or when the sensitivity and specificity of biopsy were both lower than expected.

Conclusion:

The use of biopsy to guide treatment decisions for small incidentally detected renal tumors is cost-effective and can prevent unnecessary surgery in many cases.

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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 12980 deaths and 57760 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).

Advances in Knowledge

- Risks imposed by empiric surgery, in most circumstances, equal or exceed risks of renal mass biopsy, including the probability of a false-negative result and that of biopsy track seeding with malignant cells.
- The effectiveness of renal mass biopsy in directing further treatment decisions is largely driven by a high prevalence of benign tumors and indolent cancers, which results in less aggressive treatment paradigms being favored.

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 radio-frequency 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.

Implication for Patient Care

- The use of renal mass biopsy to guide treatment decisions for small renal tumors is cost-effective relative to empiric surgical treatment and can prevent unnecessary surgery in many patients.

Materials and Methods

D.A.G. received a research grant from Valleylab (Boulder, Colo), but funding was not for this study.

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.

We performed our analysis under guidelines issued by the Panel on Cost-Effectiveness in Health and Medicine (16). We used a lifetime horizon and invoked a quasi-societal perspective; that is, costs of disease management were included, but time costs to the patient were not. Life expectancy was measured with quality-adjusted life-years (QALYs), and future costs and QALYs were discounted (16). Strategies were compared in an incremental cost-effectiveness analysis (16). If one strategy had more QALYs and fewer costs than the other, it “dominated” the other. If not, an incremental

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Abbreviations:

BCE = base-case estimate
ICER = incremental cost-effectiveness ratio
NSS = nephron-sparing surgery
QALY = quality-adjusted life-year
RCC = renal cell carcinoma

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cost-effectiveness ratio (ICER) was calculated (change in cost divided by change in QALYs), and strategy preference was determined on the basis of a \$75 000-per-QALY societal willingness-to-pay threshold.

Importantly, as we have discussed previously, the use of a single willingness-to-pay threshold for policy decisions is not standard practice in the United States (17–20). The \$75 000-per-QALY threshold was chosen within commonly accepted levels (\$50 000–\$100 000 per QALY) (21–24) to enable cost-effectiveness evaluation at the population level.

Building a Model to Estimate Outcomes after Renal Mass Biopsy and Surgery

We developed a Markov model to estimate life expectancy and lifetime costs for 65-year-old men with incidentally detected renal tumors (≤ 4 cm) who, for initial tumor management, underwent either renal mass biopsy or empiric surgery. It was assumed that patients did not have metastatic disease at the time of diagnosis on the basis of clinical and imaging work-up. A simplified model schematic is provided in Figure 1. The model was constructed by using commercially available software (TreeAge Pro 2009; TreeAge Software, Williamstown, Mass). The age of 65 was chosen based on the national median age at RCC diagnosis (25). Men were considered in the base-case analysis because of their greater RCC incidence (25).

In the primary (base-case) analysis, we compared outcomes consequent to each strategy by using best-available model input estimates (Tables 1–3). Stability of results over changes in model estimates was evaluated in secondary (sensitivity) analysis. Below, we describe basic assumptions inherent to the structure of our decision model.

Renal Mass Biopsy as a Management Strategy

In the biopsy strategy, patients with true- or false-positive biopsy results underwent NSS (Fig 1). Patients with nondiagnostic (inadequate or indeterminate) biopsy specimens also underwent NSS, under the assumption that malignancy could not be excluded.

Figure 1

Figure 1: Simplified schematic of decision model. Two management strategies were considered for initial management of an imaging-detected tumor: renal mass biopsy or empiric NSS. This schematic demonstrates how the consequences of opting for one strategy over another were modeled in our analysis. CT = computed tomography.

Patients who experienced biopsy track seeding with malignant RCC were assumed to have a subsequent course that was identical to patients with metastatic disease. This likely biased against biopsy because track seeding likely does not have such catastrophic results in all patients (12). However, without adequate data to inform the long-term sequelae of this rare event, we incorporated its worst-case consequences.

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.

Table 1

Parameter Estimates for Base-Case Analysis and Sensitivity Analysis

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

Note.—BCE = base-case estimate.

* Indeterminate or insufficient specimen.

[†] A yearly probability was reported for simplicity in interpretation, but values used in the model were adjusted to account for cumulative probability of tumor growth at each surveillance point during the 5-year surveillance.

[‡] Refer to Materials and Methods for details on selection and derivation.

[§] Refer to previously published model (17) for further parameter details.

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.

In eight studies that reported outcomes of patients who opted for imaging surveillance of a known renal mass, in 29% (137 of 475) of these cases,

Table 2

Costs and Utilities for Base-Case Analysis and Sensitivity Analysis

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%

* Unless otherwise specified, data are given in 2007 U.S. dollars.

[†] Sensitivity ranges extended to test thresholds beyond which a change in our analysis results (strategy preference) could occur.

[‡] Current Procedural Terminology code 74170.

[§] Assumed to be equivalent to NSS.

^{||} This health-state cost for renal cancer was extrapolated from the setting of metastatic colon cancer, as detailed in our previously published model (17).

[#] A discount rate was applied to all future costs and QALYs per guidelines from the Panel on Cost-Effectiveness in Health and Medicine (16).

Table 3

Renal Tumor Surveillance Studies Used in the Decision Model

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)

* Majority of tumors were incidentally detected. Combining 7 series in which the mode of detection was specified (38,39,41–45), incidental detection was reported in 90% (279/311) of cases. For this statistic, three institutions reported mode of detection on a per patient (instead of a per tumor) basis (38,41,44).

[†] Although growth data were reported, the percentage of tumors that grew during follow-up was not reported; thus, data from this study could not be incorporated for this statistic.

[‡] Follow-up data from 89 patients in this study were included. Values in this study were reported per patient, not per tumor; thus, per patient values were incorporated in summary statistics. We did not incorporate data from additional patients mentioned in this study due to lack of available institutional radiographic follow-up, as noted by the study's authors (38).

[§] Medians were reported instead of means. Therefore, for this study, median values were incorporated in summary statistics.

^{||} Calculated values are weighted to account for differences in the number of cases per series.

surveillance was terminated and tumors were treated with surgery or ablation (38–45). We therefore conservatively assumed that 29% of tumors that grew at each surveillance point would be treated surgically but varied this assumption widely in sensitivity analysis.

Biopsy Test Performance in the Model

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.

Modeling Outcomes of Patients Treated with NSS

In our model, patients' long-term outcomes were estimated by using Markov submodels. Here, we discuss the Markov submodels that we used to estimate post-NSS outcomes. Regardless of whether NSS was pursued upon tumor detection (such as in the empiric surgery strategy) or as a consequence of biopsy results or tumor growth during CT surveillance, health outcomes after NSS were modeled identically (Fig 1).

For patients found to have RCC at surgery, life expectancy was estimated in a way similar to that described in our previous publication (17) by using a Markov submodel that accounted for the possibility of local RCC recurrence, metastatic disease, and all-cause age-specific risks of mortality. Importantly,

in our current model, we incorporated a surgical mortality rate of 1.6% (14 of 899) for NSS based on a systematic review by Uzzo and Novick (37). Knowing that this estimate was reported in 2001, we reduced it to zero in sensitivity analysis to address the possibility that contemporary operative mortality rates from NSS could be lower. Other updates made to our previous model are detailed in Appendix E1 (online). Patients that had benign tumors at surgery entered a separate Markov submodel where they were susceptible only to age-specific risks of mortality until death (54). For all patients, life-years were quality-adjusted based on age (59).

Modeling Outcomes of Patients with Biopsy-Negative Tumors

We developed additional Markov submodels to estimate the quality-adjusted life expectancy of patients with true- or false-negative biopsy results (Fig 1). In these submodels, we incorporated data reported from the majority of published observational series in which tumors were managed by imaging surveillance instead of immediate surgery (Table 3). Excluded studies were limited to studies with a mean tumor size greater than 4.5 cm because larger tumors, on average, have more aggressive behavior than those under consideration in our model (7) and studies in which all patients in a retrospectively selected sample ultimately underwent surgery. Since surgery is usually performed when metastases are not suspected, we were concerned that by incorporating such studies, we would overestimate indolence in biopsy-negative tumors.

In six studies, reported tumor growth during surveillance was observed in 72% (293 of 409) of cases during a weighted mean follow-up of 31 months (38–43) (Table 3). In eight studies, metastasis during surveillance was observed in 1% (five of 475) of cases during a weighted mean follow-up of 33 months (38–45) (Table 3).

We incorporated these data as follows. At each CT surveillance interval, patients with benign or malignant biopsy-negative tumors were susceptible to CT-detected tumor growth. We

used a standard exponential assumption to predict the proportion of tumors that would grow, p_{grow} , over a given time interval, t : $p_{\text{grow}} = 1 - e^{-(\ln(1-0.72)/31)t}$ (65,66).

To determine the probability of developing metastatic disease, we first adjusted the observed probability of metastasis (five of 475 cases) to account for the expected prevalence (77%) of malignant tumors in the surveillance population: $5/(475 \cdot 0.767) = \text{five of } 364 \text{ cases} = 0.014$ (7). We questioned whether this estimate could be lower than expected owing to two primary factors. First, a selection bias could be present, causing tumors followed by surveillance to be more indolent, on average, than those that are immediately surgically resected. Second, the average follow-up surveillance period in the literature was intermediate in length (33 months) (38–45,67). Considering these factors, we calculated the 95% confidence interval surrounding the adjusted value (0.014; 95% confidence interval: 0.032, 0.004) and used the upper boundary (ie, 0.032) for further calculations, thereby assuming a higher probability of metastasis for biopsy-negative RCC than reported in the literature. We then invoked an exponential assumption to calculate the probability of metastasis, $P(\text{mets})$, over a given time interval, t : $P(\text{mets}) = 1 - e^{-(\ln(1-0.032)/33)t}$ (65,66).

As mentioned above, in the base-case analysis, we assumed that a proportion of patients who had any growth of a biopsy-negative tumor would undergo NSS (46–51) (Table 1). Patients with false-negative results (biopsy-negative RCC) who did not undergo NSS remained susceptible to development of metastases, in addition to age-specific mortality risks. Patients with true-negative results (benign tumors) were susceptible only to age-specific mortality risks. During and after surveillance, for all patients, life-years were quality-adjusted based on age (59).

Costs

Model cost estimates are included in Table 2. Costs were converted to 2007 U.S. dollars by using the medical care component of the Consumer Price Index.

Costs of percutaneous renal mass biopsy were based on costs reported by Silverman et al (55) for performing percutaneous biopsy of masses in the retroperitoneum. As noted above, we accounted for biopsy complications by incorporating additional associated costs, as reported by Silverman et al (55). Details regarding elicitation of cost values are provided in Appendix E1 (online).

Costs of follow-up CT examinations performed after a negative biopsy or NSS were derived from the applicable Current Procedural Terminology code (Table 2). CT surveillance patterns after a negative biopsy were discussed above. After NSS, we assumed CT would be performed each year for 5 years, and then thrice over the next 5 years, according to institutional experience.

Costs of NSS and of locally recurrent and metastatic RCC were applied as in our previous model (17). General age-specific expenditures for medical care were applied to all patients based on published data to account for non-RCC-related health expenses beginning at the time of tumor detection and continuing until death (57).

Sensitivity Analysis

Sensitivity analysis was performed to evaluate the effects of varying model parameter estimates on results. Sensitivity ranges for each parameter are included in Tables 1 and 2. One-way sensitivity analysis was performed on all model variables. During one-way analysis, we extended certain ranges to identify thresholds beyond which a change in our analysis results (strategy preference) could occur. The thresholds identified included: the lower limit of NSS costs and the upper limits of biopsy costs, with and without associated complications.

Two-way analysis was performed on the following variable pairs and ranges: the renal mass biopsy sensitivity and specificity (each was varied from 50% to 100%), the prevalence of RCC in detected tumors (varied from zero to 100%), and the probability of metastasis for a biopsy-negative RCC (yearly probability varied from 0.006 to 0.018, which was 0.5–1.5 times the BCE) (Table 1).

Model Validation

To our knowledge, long-term outcomes from a large patient cohort with biopsy-negative tumors have not been reported. We therefore could not identify an ideal data source to validate our predicted life expectancy for patients with biopsy-negative RCC. The predicted life expectancy of patients that underwent NSS for RCC in our current model was validated as described previously (17). We used the 5-year cancer-specific survival (96.5%) reported for patients with surgically resected RCC no larger than 4 cm from a large observational study to estimate life expectancy from this independent data source (6). We then compared this value to the post-NSS life expectancy estimate from our model.

Results

Model Validation

A 15.2-year life expectancy after NSS was calculated by using the post-NSS Markov submodel without discounting or quality adjustment. This was within 2% of that calculated by using the validation source (14.9 years) (6). For the purposes of our analysis, this difference was adequate for validation of the post-NSS submodel.

Base-Case Cost-effectiveness Analysis

Base-case results are summarized in Table 4. The biopsy strategy yielded a minimally greater life expectancy (4 days) with a lower lifetime cost (\$3466) than did empiric NSS. Therefore, the biopsy strategy dominated empiric NSS.

Sensitivity Analysis

One-way sensitivity analysis.—The biopsy strategy dominated empiric NSS across the majority of sensitivity ranges tested. Scenarios in which biopsy no longer dominated empiric NSS or was no longer cost-effective relative to empiric NSS (based on an assumed willingness-to-pay threshold of \$75 000 per QALY) are listed in Table 5 and discussed below.

The biopsy strategy no longer dominated empiric NSS when the yearly probability of metastasis for unresected

Table 4

Cost-Effectiveness Analysis Results

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

Note.—Empiric NSS was found to be dominated by biopsy. QALE = quality-adjusted life expectancy.

* A discount rate was applied to all future costs and QALYs per guidelines from the Panel on Cost-Effectiveness in Health and Medicine (16).

† Approximately 4 days.

RCC increased from 0.012 (BCE) to greater than 0.016, when the NSS mortality rate decreased from 0.016 to less than 0.01, and when renal mass biopsy sensitivity decreased from 0.90 to less than 0.78 (Table 5). However, the biopsy strategy remained cost-effective relative to empiric NSS (ICER of NSS relative to biopsy was more than \$75 000 per QALY) throughout the remainder of the tested ranges for each of these three parameters. Of note, when the NSS mortality rate was reduced to 0%, the biopsy strategy was still considered cost-effective relative to NSS on the basis of the assumed \$75 000 per QALY willingness-to-pay threshold.

Empiric NSS was more cost-effective than the biopsy strategy if the prevalence of RCC among small renal masses increased from 77% (BCE) to greater than 98% (ICER of NSS relative to biopsy was less than \$75 000 per QALY). If RCC prevalence was greater than 87% but less than or equal to 98%, the biopsy strategy did not dominate empiric NSS but remained cost-effective (ICER of NSS relative to biopsy was more than \$75 000 per QALY).

When extending certain sensitivity ranges to identify thresholds beyond which a change in our analysis results could occur, we found that in the following scenarios the biopsy strategy was no longer cost-effective relative to empiric NSS (ICER of biopsy relative to empiric NSS was more than \$75 000 per QALY): NSS costs of less than \$6963; biopsy costs, without complications, of more than \$5141; and biopsy

Figure 2

Figure 2: Plot of two-way sensitivity analysis of biopsy sensitivity and specificity. When biopsy sensitivity and specificity are high, as is typical (BCE: sensitivity, 90%; specificity, 100%), the biopsy strategy provides greater life expectancy (green). Blue = empiric NSS provides greater life expectancy.

costs, with complications, of more than \$93 021 (Table 5). Under the following conditions, the biopsy strategy no longer dominated empiric NSS but remained cost-effective: NSS costs of less than \$11 895 but at least \$6963; biopsy costs, without complications, of more than \$4291 but less than or equal to \$5141; and biopsy costs, with complications, of more than \$74943 but less than or equal to \$93 021 (Table 5).

Two-way sensitivity analysis.—In two-way sensitivity analysis, when both renal mass biopsy sensitivity and specificity were widely simultaneously varied, these parameters had to be substantially reduced in order for empiric NSS to yield a greater life expectancy, as shown in Figure 2.

When two factors that govern the aggressiveness of the tumors in our model (RCC prevalence and the yearly probability of metastasis from unresected RCC) were simultaneously varied, only with extremely high estimates of both did empiric NSS yield a greater life expectancy than did biopsy, as shown in Figure 3.

Discussion

The role of renal mass biopsy in managing renal tumors has been controversial, primarily owing to two biopsy risks: the

Table 5

Results of One-Way Sensitivity Analysis

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

* Based on an assumed societal willingness-to-pay threshold of \$75 000 per QALY. Biopsy was not considered cost-effective vs empiric NSS if the ICER of biopsy was >\$75 000 per QALY vs NSS or if the ICER of NSS was <\$75 000 per QALY vs biopsy.

[†] Reference 7.

[‡] References 38–45.

[§] Biopsy cost-effective throughout tested range. DNE = does not exist.

^{||} Reference 37.

[#] Refer to Materials and Methods for details on selection of this parameter.

** Sensitivity ranges extended to test thresholds beyond which a change in our analysis results (strategy preference) could occur. See Materials and Methods for further details.

Figure 3

Figure 3: Plot of two-way sensitivity analysis of parameters that determine tumor aggressiveness. Biopsy yields a greater life expectancy (green) over most of the parameter space tested. When tumors are assigned more aggressive features (ie, higher prevalence of malignancy and propensity to metastasize) than would be typically expected (BCE: yearly probability of metastasis for a biopsy-negative RCC, 0.012; prevalence of RCC among tumors, 0.77), then empiric NSS yields a greater life expectancy (blue).

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.

Our study had several limitations, many of which are common to all decision-analytic studies. First, there were limited data available to model the behavior of biopsy-negative renal tumors

(38–45,67). Furthermore, adequate data were not available to validate our model predictions for patients with biopsy-negative RCC using an independent data source. To account for any potential underestimation of the probability of metastasis of biopsy-negative RCC, instead of incorporating the observed probability of metastasis directly into our analysis, we used the upper boundary of the 95% confidence interval surrounding this estimate to inform our model. Even so, the biopsy strategy dominated empiric NSS, yielding a comparable life expectancy at a lower cost.

Second, modeling a surveillance strategy for biopsy-negative tumors was difficult because there are no accepted guidelines for surveillance endpoints (eg, tumor growth rates) that should trigger a practitioner to curtail surveillance and recommend treatment. In practice, tumor growth often guides the clinical decision to terminate surveillance and undergo treatment. Interestingly, tumor growth has not been shown to be a significant predictor of malignancy, although, as noted, reported surveillance data remain limited in extent (61). As a starting point in our base-case analysis, we assumed that at each surveillance interval 29% of patients with a growing biopsy-negative tumor would elect to have surgery (38–45,67). Even when this value was varied widely, the biopsy strategy dominated empiric NSS, resulting in comparable life expectancy at a lower lifetime cost.

Third, our analysis best applies to tumors that, if malignant, are highly likely to be RCC. We did not account for urothelial malignancy, lymphoma, rarer primary renal malignancies (eg, capsular sarcoma), metastatic disease, or infection as potential etiologies of a small renal mass. If no known primary nonrenal malignancy is present and there is no evidence of urinary tract infection, then small renal masses are rarely the above entities (68). For a subset of small renal masses, however, both urothelial malignancy and RCC are diagnostic considerations on the basis of imaging appearance. In this tumor subset, as discussed above, a ureteroscopic approach to tissue sampling should be considered.

Fourth, to inform costs in our analysis, we primarily used data from peer-reviewed published literature as opposed to Medicare reimbursement values. The advantage of our approach is that many cost estimates could be more specific to our analysis than if we had exclusively used reimbursement values based on Current Procedural Terminology and Diagnosis-Related Group codes, which cover broad procedure types and disease categories. The disadvantage of our approach is that individual published analyses are heterogeneous by nature and have elements that may not be generalizable, ranging from costing methods, to hospital operations, to patient populations. This type of heterogeneity had the greatest potential effect on our analysis when considering the procedural costs that we applied for NSS and biopsy. To address the uncertainty of these cost estimates, we varied them widely in sensitivity analysis and determined the effects on our analysis results. We found that, on average, the cost of biopsy would need to be higher than \$5141 and that of NSS would need to be lower than \$6953 in order for the biopsy strategy to no longer be cost-effective relative to empiric NSS. We also found that the cost of a biopsy with associated complications, on average, would have to be higher than \$93021 in order for the biopsy strategy to no longer be cost-effective. Because the true costs of performing a procedure are variable, the potential cost savings that we report for the biopsy strategy (\$3466) in our base-case analysis is not, in itself, as important as are the trends observed and insights gained when repeating our analysis under different cost scenarios.

Fifth, the estimated NSS mortality rate that we used in our model (1.6%) was reported in 2001 and was based on pooled institutional experiences published before that time (37). To address the possibility that contemporary NSS mortality rates could be lower, we varied this estimate substantially to determine the potential effects on our results. We found that below a rate of 1%, the NSS strategy would yield a slightly higher quality-adjusted life expectancy

than biopsy but that it would still not be considered cost-effective (given an assumed \$75 000 per QALY willingness-to-pay threshold), even with a surgical mortality rate of 0%.

Imaging-guided minimally invasive therapies—in particular, radiofrequency ablation and cryoablation—are now commonly being used to treat small renal tumors in patients who have multiple comorbidities, reduced life expectancy, or limited renal parenchymal reserve (15). When ablative therapies are used, preprocedural biopsy offers the only opportunity to confirm malignancy but is not uniformly obtained (15,69). Decision-analytic techniques would allow for the hypothetical comparison of an empiric ablative strategy, in which biopsy was never performed preprocedurally, with a strategy in which biopsy was routinely performed to triage patients to ablation versus surveillance. This type of analysis would be analogous to our current study but would require consideration and incorporation of procedural risks, costs, and outcomes that are specific to ablative therapies, as opposed to NSS. Importantly, a unique aspect of using ablation to treat tumors is that, without preprocedural biopsy, most patients will never know whether or not their tumor was malignant and, thus, their true likelihood of cancer recurrence. Patient preferences merit rigorous study and consideration in an analysis of empiric ablation because the extent to which patients would be willing to live with this approach could very well drive its viability from a cost-effectiveness perspective.

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.

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