Personalized Treatment for Small Renal Tumors: Decision Analysis of Competing Causes of Mortality

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Purpose: To compare the effectiveness of personalized treatment for small (≤4 cm) renal tumors versus routine partial nephrectomy (PN), accounting for various competing causes of mortality.

Materials and Methods: A state-transition microsimulation model was constructed to compare life expectancy of management strategies for small renal tumors by using 1 000 000 simulations in the following ways: routine PN or personalized treatment involving percutaneous ablation for risk factors for worsening chronic kidney disease (CKD), and otherwise PN; biopsy, with triage of renal cell carcinoma (RCC) to PN or ablation depending on risk factors for worsening CKD; active surveillance for growth; and active surveillance when MRI findings are indicative of papillary RCC. Transition probabilities were incorporated from the literature. Effects of parameter variability were assessed in sensitivity analysis.

Results: In patients of all ages with normal renal function, routine PN yielded the longest life expectancy (eg, 0.67 years in 65-year-old men with nephrometry score [NS] of 4). Otherwise, personalized strategies extended life expectancy versus routine PN: in CKD stages 2 or 3a, moderate or high NS, and no comorbidities, MRI guidance for active surveillance extended life expectancy (eg, 2.60 years for MRI vs PN in CKD 3a, NS 10); and with Charlson comorbidity index of 1 or more, biopsy or active surveillance for growth extended life expectancy (eg, 2.70 years for surveillance for growth in CKD 3a, NS 10). CKD 3b was most effectively managed by using MRI to help predict papillary RCC for surveillance.

Conclusion: For patients with chronic kidney disease and small renal tumors, personalized treatment selection likely extends life expectancy.

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Personalized decision making has been proposed to improve the treatment of tumors that have variable risk of progression. One example is prostate cancer, and an analogous disease may exist in small renal tumors (≤4 cm) (1,2). Renal cortical tumors are most often discovered as early stage incidental lesions, and a substantial proportion are benign or indolent malignancies (3–6). The standard approach has been to treat these tumors with surgical resection for the best possible oncologic outcomes (7–9). Alternative forms of treatment are gaining increasing recognition and active surveillance may be considered in patients with limited life expectancy or advanced comorbidities. However, to our knowledge there are no consensus guidelines or decision support tools for weighing of multiple factors that affect health outcomes, and active surveillance may therefore remain underused when compared with the benefits and harms of all treatment options.

The management of small renal tumors in this generally older population is complicated by risk of death from non-oncologic causes that are competing risks related to medical comorbidities. In particular, chronic kidney disease (CKD) is prevalent in this patient population and leaves patients susceptible to worsened renal function and associated cardiovascular mortality (10,11). Further guidance is needed to synthesize the benefits and harms of management options, including imaging-based active surveillance to monitor lesion growth or signs of progression, biopsy-based management, and percutaneous ablation (9). Furthermore, MRI has been shown to provide reliable identification of one indolent subtype of renal cell carcinoma (RCC), papillary RCC (12–14). Such risk stratifying information could potentially provide guidance when considering the benefits and harms of active surveillance (12).

A comparative analysis accounting for different risks of the renal tumor, patient comorbidities, and treatment type is needed to assess the potential for personalized treatment decisions (15–17). Decision-analytic modeling has been used to compare treatment strategies for numerous conditions wherever trial data are not available or do not allow for direct comparisons of interventions (18–20). Given the lack of randomized trial data to date regarding partial nephrectomy (PN) versus active surveillance, and the need for guidance on how surveillance can be designed to balance benefits and harms for a
for postoperative renal functional decline (21). Our purpose was to compare the effectiveness of personalized treatment for small (≤4 cm) renal tumors versus routine PN by accounting for various competing causes of mortality. We hypothesized that patients with any elevated mortality risk related to worsening CKD and other comorbidities would benefit most from nonsurgical management.

**Materials and Methods**

**Model Overview**

A state-transition microsimulation model was used to project life expectancy over routine partial nephrectomy in patients with small renal tumors and risk factors for worsening chronic kidney disease. Given the lack of randomized trials and the complexity of weighing competing risks for mortality, trial design and clinical decision-making can be supported by the Renal Anatomy and Function for Indeterminate Renal Mass (ReAFFIRM) microsimulation model.

MRI that helps to predict papillary renal cell carcinoma has potential to improve long-term health outcomes by guiding consideration for active surveillance, and merits prospective evaluation.

### Abbreviations

CCI = Charlson comorbidity index, CKD = chronic kidney disease, NS = nephrometry score, PN = partial nephrectomy, RCC = renal cell carcinoma, ReAFFIRM = Renal Anatomy and Function for Indeterminate Renal Mass

### Summary

Health outcomes for small renal tumors (≤4 cm) have potential for substantial improvement with personalized treatment selection, which explicitly accounts for competing risks of mortality.

### Implications for Patient Care

- Personalized treatment selection offers substantial extension of life expectancy over routine partial nephrectomy in patients with small renal tumors and risk factors for worsening chronic kidney disease.
- Given the lack of randomized trials and the complexity of weighing competing risks for mortality, trial design and clinical decision-making can be supported by the Renal Anatomy and Function for Indeterminate Renal Mass (ReAFFIRM) microsimulation model.
- MRI that helps to predict papillary renal cell carcinoma has potential to improve long-term health outcomes by guiding consideration for active surveillance, and merits prospective evaluation.

heterogeneous patient population, we constructed a decision-analytic model to synthesize the evidence and compare a number of strategies. The simulated population included variable severity of CKD, comorbidity status, and tumors with variable malignant potential and anatomic complexity as a risk factor for postoperative renal functional decline (21). Our purpose was to compare the effectiveness of personalized treatment for small (≤4 cm) renal tumors versus routine PN by accounting for various competing causes of mortality. We hypothesized that patients with any elevated mortality risk related to worsening CKD and other comorbidities would benefit most from nonsurgical management.

**Materials and Methods**

**Model Overview**

A state-transition microsimulation model was used to project life expectancy over routine partial nephrectomy in hypothetical patients with clinical stage T1a (≤4 cm; small) renal masses. Renal tumors were benign or malignant, and risks of disease progression were on the basis of the type of treatment (22–25). Specifically, patients with malignancies were susceptible to local recurrence or metastatic disease after nephron-sparing therapies, and to tumor growth and metastatic disease at active surveillance (25,26). The model simulated estimated glomerular filtration rate decline and different baseline CKD stages and was calibrated to fit survival data from large patient-based surgical series (10,11).

Renal functional decline after PN was a function of the baseline CKD stage and the anatomic complexity of the tumor according to the radius, exophytic/endophytic properties, nearness...
to collecting system or sinus, anterior/posterior, location relative to polar lines (referred to as RENAL) nephrometry score (NS), which has been shown to predict parenchymal and functional loss after PN (27–29). Technical details of modeling renal functional decline and CKD-related mortality risks were described previously (21), and included model construction, calibration, and validation; this preparatory study involved simulated combinations of tumor NSs and CKD stages to identify whether the more effective nephron-sparing treatment option was PN or percutaneous thermal ablation (21). The favored nephron-sparing therapy was then incorporated into all personalized treatment strategies for the current model (Fig 1). For example, with the biopsy strategy, ablation rather than PN extended life expectancy for patients with RCC, stage 3a CKD, and NS higher than 7; therefore, ablation was the prescribed treatment.

Next, the baseline renal functional status, risk for worsened renal function after surgery, and overall comorbidity status were combined with further risk stratification for personalized treatment. Potential oncologic risk was assessed through biopsy, active surveillance for growth, or prediction at MRI of papillary RCC, and potentially indolent tumors that were identified in accordance with each testing strategy were diverted away from PN to further protect from mortality related to CKD. The final model compares usual care (ie, PN) and a number of strategies representing personalized treatment pathways (Fig 2), and is called the Renal Anatomy and Function for Indeterminate Renal Mass (ReAFFIRM) treatment model. The model was built by using software (TreeAge Pro 2015, TreeAge Software, Williamstown, Mass; S.K.K., with 6 years of experience). Patients were susceptible to surgical, CKD-associated, and cancer-specific mortality, and all-cause mortality on the basis of the Charlson comorbidity index (CCI) (30). Major parameters in the model (Tables 1, 2) and health states for malignant masses that begin with active surveillance are presented in Figure E1(online).

![Diagram](image_url)

**Figure 2**: Simplified schematic of decision-analytic model of small renal tumor management and consequent events. Malignant lesions watched for growth during imaging surveillance had potential to metastasize, while benign lesions were resected if demonstrating rapid growth. aIn active surveillance for growth, a threshold for growth was used to determine test positivity, and growth rates across a distribution were applied to lesions with overall prevalence of 75% malignancies as reported in the literature. True-positive rate for MRI helping to predict papillary renal cell carcinoma was calculated by using the Bayes revision for test sensitivity and reported proportion of papillary renal cell carcinoma among surgically resected stage T1a renal masses. bFalse-positive rate for biopsy assumed to be 0. cAblation for patients with either stage 3b chronic kidney disease or nephrometry score of 7 or greater with stage 3a chronic kidney disease. dTrue-positive rates at empirical treatment determined by reported proportion of malignant lesions among pathologic stage T1a renal tumors.

| Table 1: Patient and Tumor Characteristics Represented in the Model |
|-------------------------|-----------------|-----------------|
| Parameter               | Possible Value  | Values Represented in Model Analyses |
| Patient age (y)         | All patients over 18 years | 50, 55, 60, 65, 70 |
| Charlson comorbidity index (31) | Sum of weighted scores, starting with 0 | 0, ≥ 1 |
| Stages of chronic kidney disease (32) | All stages | All stages |
| 1, normal               |                 |                 |
| 2, mild loss of function|                 |                 |
| 3a, mild-to-moderate loss of function| | |
| 3b, moderate-to-severe loss of function| | |
| 4, severe loss of function| | |
| 5, end-stage disease    |                 |                 |
| Nephrometry score (33)  | 4–10 for renal tumors ≤ 4 cm | All values for renal tumors ≤ 4 cm |

Note.—Patient age was defined as age in years, Charlson comorbidity index is the weighted index of comorbidity burden for predicting the patient’s risk of mortality, stage of chronic kidney disease is the classification system for severity of chronic kidney disease, and the nephrometry score is the scoring system for anatomic complexity of renal tumor.
CT-based active surveillance with nephron-sparing treatment for growing lesions; and (e) active surveillance for presumed papillary RCC on the basis of contrast agent–enhanced MRI, with nephron-sparing treatment for all other tumors. For strategies b–e, the selection of nephron-sparing treatment (PN or ablation) was on the basis of whether PN or percutaneous ablation was favorable for the CKD stage and NS (21).

In the biopsy strategy, biopsy occurred at the start of the model, just after discovery of the small renal tumor.

| Table 2: Major Parameter Values for Model Inputs |
|-----------------------------------------------|
| Parameter                                      | BCE       | Sensitivity Analysis Range |
| Patient age (y)                                | 65 (34)   | 50–70                  |
| Patient sex                                    | Male (34) | Female                 |
| Probability of mortality from PN              | 0.016 (35)| 0–2 × BCE              |
| Probability of mortality from ablation        | 0.001 (Expert opinion; none reported) | 0–2 × BCE   |
| Annual probability of local recurrence after PN| 0.0031 (25,36–39) | 0.5–1.5 × BCE |
| Annual probability of local recurrence after ablation | 0.0058 (24) | 0.5–1.5 × BCE |
| Annual probability of developing metastases from recurrent RCC | 0.2 (34,40) | 0.5–1.5 × BCE |
| Annual probability of death due to metastatic RCC | 0.27 (41) | 0.5–1.5 × BCE |
| Annual probability of growth during active surveillance | 0.38 (42–44) | 0.5–1.5 × BCE |
| Proportion of nonbiopsied growing tumors undergoing nephron-sparing treatment for growth | 1.0 (42–45) | 0.29–1.0 (42–45) |
| Proportion of biopsy-negative, growing tumors undergoing nephron-sparing treatment for growth | 0.10 (46) | 0.5–1.5 × BCE (42–45) |
| Annual probability of metastasis during active surveillance of RCC | 0.02 (8,17,47) | 0.01–0.05 (17,26,42,45) |
| Annual age-specific probability of death from unrelated causes | U.S. life tables (48) | 0.5–1.5 × BCE |
| Annual eGFR decrease after PN (%)             | 1.5, 2.5 per each point increase in NS* (27,28) | 0.5–1.5 × BCE |
| Annual eGFR decreased by CKD stage after ablation (mL/min/1.73 m²) | 1.2 (49,50) | 0–3 × BCE (51) |
| Hazard ratio for mortality related to CKD stage in patients who underwent ablation | Stage 1, 2 | 1 (52) |
| Hazard ratio for mortality related to CKD stage in patients who underwent PN | Stage 1 | 1 (10) |
| Mean Charlson comorbidity index                | 0.4 (53)  | 0–1.0 (53)             |
| Hazard ratio of mortality for Charlson comorbidity index of ≥ 1 | 1.33 (30) | 1.0–2.0 |
| Probability of malignancy                     | 0.75 (54) | 0.5–1.0 (55)           |
| Probability of papillary RCC among RCC        | 0.15 (8,56) | 0.07–0.22 |
| MRI sensitivity for papillary RCC             | 0.793 (12) | 0.591–0.890 (13,57,58) |
| MRI specificity for papillary RCC             | 0.913 (12,13) | 0.799–0.981 (13,57,58) |

Note.—Data in parentheses are source reference numbers. Men and women age 50–70 years were represented in the sensitivity analysis. BCE = base case estimate, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, PN = partial nephrectomy, RCC = renal cell carcinoma.

* Weighted mean estimated glomerular filtration rate decrease calculated for use in model.
† On the basis of the hazard ratio for baseline estimated glomerular filtration rate range of 60–75 mL/min/1.73 m² in source.

## Modeled Strategies

The ReAFFIRM model compares life expectancy across the following strategies: (a) initial intervention with PN for all patients (standard treatment); (b) PN for those at low risk for excess mortality related to renal functional decline and initial treatment with percutaneous ablation for patients at risk (ie, stage 2 or 3a CKD and complex tumor anatomy, or stage 3b CKD and any tumor anatomy); (c) renal mass biopsy, with triage of cancers to ablation or PN on the basis of CKD and tumor anatomy; (d)...
results that were positive for malignancy or indeterminate were treated on the basis of CKD stage and NS. A low risk of biopsy tract seeding was represented (59). Biopsy sensitivity and specificity for detection of malignancy were applied from recent literature (60) for renal tumors that were ≤4 cm or smaller. Benign results were monitored with imaging surveillance for 5 years, and 10% eventually underwent treatment for substantial growth.

With imaging-based active surveillance, patients underwent a single-phase contrast-enhanced abdominal CT examination to monitor for lesion growth on a schedule of every 6 months for the 1st year, then yearly for an additional 4 years (9,61,62). Lesions that did not grow at the end of 5 years were assumed to be benign (or highly indolent malignancies) with no further risk of metastatic disease (26,63). The proportion of lesions (benign or malignant) that grew enough to warrant treatment was derived from the literature (42,43).

We also tested the selection of lesions for surveillance by using MRI. Contrast-enhanced MRI was used to help predict papillary RCC versus nonpapillary RCC tumors (including benign lesions, and clear cell or chromophobe RCC) because high specificity and accuracy have been reported (12,13,57). Given the general indolence of papillary RCC, these lesions were watched for growth whereas the remaining tumors were treated with nephron-sparing therapy (64).

ReAFFIRM results of life expectancy were validated against independent sources of cancer-specific and overall survival not used in the model, including a prospective registry of patients undergoing active surveillance (46), and a retrospective analysis of cancer-specific and overall mortality in patients treated for localized RCC (65). Additional validation methods specific to modeling survival with CKD were previously reported (21).

Patient Characteristics in the Model
The base case population consisted of 65-year-old men (median age of diagnosed RCC in the United States) with sufficient overall health for consideration of surgery and diagnosis of a small renal tumor (34). Additional cohorts included men and women ranging in age from 50 to 70 years (Table 1). One million microsimulations were completed for each studied cohort. CKD stages were classified according to the National Kidney Foundation definitions of estimated glomerular filtration rate values: mild or stage 2 CKD (60–89 mL/min/1.73 m²), moderate or stage 3a and 3b CKD (30–44 and 45–59 mL/min/1.73 m², respectively), and severe CKD (15–29 mL/ min/1.73 m²) (66). We derived the distribution of estimated glomerular filtration rate and CKD stages in baseline and postoperative populations from the literature (67).

Table 3: Metastatic Disease Rates for Major Renal Cell Carcinoma Subtypes

| RCC Subtype   | Annual Metastatic Rate (%) | Five-Year Cancer-Specific Survival (%) |
|---------------|---------------------------|---------------------------------------|
| Clear cell    |                           |                                       |
| All*          | 2.49                      | 91.5                                  |
| High          | 2.12                      | 92.3                                  |
| Low           | 1.90                      | 93.4                                  |
| Papillary     | 0.63                      | 97.7                                  |
| Chromophobe   | 0.89                      | 96.8                                  |
| All subtypes  | 2.07                      | 92.8                                  |

Note.— Rates were derived from fitting calibration models with Surveillance, Epidemiology, and End Results Medicare data on initially untreated lesions. RCC = renal cell carcinoma, SEER = Surveillance, Epidemiology, and End Results. *Includes tumors without known Fuhrman grade.

Tumor Characteristics in the Model
The anatomic complexity of renal tumors was represented in the model by using the RENAL NS (33). The rate of renal functional decline after PN was on the basis of reported regression formulas incorporating NSs (21,27,28). For ablation, active surveillance, and biopsy strategies, tumor anatomy did not worsen renal functional decline beyond the rate of the general population for a given age (49).

An author (S.K.K.) built a calibration model to obtain the rates of metastatic disease in patients with untreated RCC and its subtypes by using an original analysis of Surveillance, Epidemiology, and End Results cancer registry data linked with Medicare claims (E.B.E., W.B.H.). The derived metastatic rates for untreated RCC are in Table 3. The Surveillance, Epidemiology, and End Results Medicare data were used in accordance with a data use agreement from the National Cancer Institute for an earlier study of small kidney cancers, involving a minimum period of nonsurgical management of 6 months and a median follow up of 57 months (interquartile range, 43–89 months) (8).

Sensitivity Analysis
One-way and two-way sensitivity analysis varied major parameters across a range of values from the literature to assess effect on the favored strategy (Table 2). To assess the effects of parameter uncertainty, probabilistic sensitivity analysis was performed. Major input values were assigned distributions (Table E1 [online]), with distribution values reflecting stochastic uncertainty and therefore differing from one-way and two-sensitivity analyses; these distributions were sampled 10 000 times before running simulated patients, and results indicated the probability of each strategy being most favorable. An additional sensitivity analysis incorporated histologic subtype information from biopsy, which provided further risk stratification. Specifically, the biopsy strategy was modeled in an alternate form so that only histologic results of clear cell RCC resulted in initial nephron-sparing treatment.

Results

Model Validation
Life expectancy of patients was validated by using survival data reported in an independent source (not applied to the model) and showed similar results for preoperative CKD with worsening after PN (65). For example, life expectancy for patients with stage 3a CKD who were treated with PN in the ReAFFIRM model was compared with a separate smaller
validation model and source, and the results were 12.33 versus 12.30 years for stage 3a CKD in 65-year-old men, respectively. Details of model validation and results are provided in the Table E2 (online).

**Base-Case Results**
The favorability of standard treatment (ie, PN) compared with personalized treatment strategies differed according to patient and tumor characteristics. In the base case of 65-year-old men with small renal tumors, PN was superior for all patients with normal renal function. For example, in 65-year-old men with NS of 4, CCI of 0, and normal renal function, life expectancy after PN was 14.93 years, with life expectancy values and favored strategies for example subpopulations are also provided in Tables E3 and E4 (online). An algorithm also summarizes the most effective personalized treatment approaches according to patient and tumor characteristics (Fig 3).

**Optimal Personalized Treatment Approach according to Patient and Tumor Characteristics**
In patients with abnormal renal function, the best approach differed by patient and lesion characteristics (Table 4). In 65-year-old men without comorbidities (CCI, 0), MRI characterization of papillary versus nonpapillary tumor offered improved

### Table 4: Most Effective Treatment Pathway for Base Case Analysis of 65-year-old Men and Women According to Patient and Tumor Characteristics

| Parameter | Nephrometry Score | CKD Stage 1 (ie, normal) | CKD Stage 2 | CKD Stage 3a | CKD Stage 3b |
|-----------|------------------|-------------------------|-------------|-------------|-------------|
| 65-year-old men CCI score | | | | | |
| 0 | 4–5 | PN > ABL | PN > ABL | ABL > *MRI | MRI > WW |
| 0 | 6 | PN > ABL | PN > ABL | ABL > *MRI | MRI > WW |
| 0 | 7 | PN > ABL | MRI > ABL | MRI > WW | MRI > Bx |
| 0 | 8–9 | PN > ABL | MRI > ABL | MRI > WW | MRI > Bx |
| ≥1 | 4–5 | PN > ABL | PN > ABL | ABL > MRI | WW > ABL |
| ≥1 | 6 | PN > ABL | PN > ABL | ABL > Bx | WW > ABL |
| ≥1 | 7 | PN > ABL | Bx > MRI | WW > MRI | MRI > Bx |
| ≥1 | 8–9 | PN > ABL | Bx > MRI | WW > MRI | MRI > Bx |
| ≥1 | 10 | PN > ABL | Bx > MRI | WW > MRI | MRI > Bx |

65-year-old women CCI score

Note.—The top two strategies are presented for each patient subgroup. MRI indicates selection of papillary renal cell carcinoma for surveillance. Noninferiority was determined by using criterion of 7 days or less difference between life expectancy of the treatment strategies. In the biopsy and surveillance strategies, nephron-sparing treatment was selected as follows: partial nephrectomy for patients with normal renal function, and for stage 2 or 3a chronic kidney disease and nephrometry score ≤ 6, and otherwise percutaneous ablation. Strategies in parentheses indicate less than 7 days difference in life expectancy between the two strategies. The strategy that resulted in greater than 7 days difference in life expectancy compared with the next most effective strategy is indicated by > symbol. ABL = percutaneous ablation, Bx = biopsy-based treatment of cancers, CCI = Charlson comorbidity index, CKD = chronic kidney disease, PN = partial nephrectomy, WW = watchful waiting (ie, surveillance with treatment of growing lesions).

*MRI prediction of nonpapillary tumors led to treatment with PN based on low NS category of 4–6, and otherwise ablation.

† Routine ablation and biopsy-based management resulted in life expectancies with difference of less than 7 days.
Sensitivity Analysis

In univariable sensitivity analysis for the overall population of 65-year-old men with small renal tumors, results were most sensitive to rates of renal function decline, CKD-related mortality, and pretest probability of a benign lesion (Table 5). Life expectancies and most effective strategies by tested ages and CKD stages are in Tables E3 and E4 (online). In patients with CCI of 0 with normal renal function, PN was optimal even after an approximate postoperative 30% reduction in estimated glomerular filtration rate as may be observed with radical nephrectomy (68,69). When the local recurrence rate after ablation was varied to be the same value as PN with all other assumptions held constant, patients with normal renal function were most effectively treated with ablation. At two-way sensitivity analysis, the pretest probability of a malignant lesion and renal functional loss after PN were concurrently varied for patients with stage 3a CKD and NS of 10, and showed that biopsy leading to PN for all RCC was not favorable unless the pretest probability of malignancy was less than 15%.

Probabilistic sensitivity analysis showed stability in results after incorporation of distributions reflecting uncertainty around the accuracy of MRI in addition to all major parameters; for example, in 65-year-old men with stage 3a CKD and NS 10, the model favored MRI selection for active surveillance in 85% of iterations (vs 15% for surveillance for growth). In an additional
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and women with comorbidities (CCI \( \geq 1 \)) and mild CKD (stage 2) with moderate to high tumor anatomic complexity. However, an alternative use of biopsy for risk stratification, in which RCC histologic subtype guides therapy, was favorable over all other strategies in most patients with CKD stage 3 or comorbidities. A Surveillance, Epidemiology, and End Results Medicare analysis of initially untreated stage T1a RCC yielded differences in the 5-year metastatic rates among RCC subtypes, and therefore biopsy-based treatment of the more aggressive clear cell tumors acted as a more accurate alternative to MRI guidance for surveillance.

**Discussion**

By mathematically weighing competing oncologic and nononcologic risks for mortality, we identified personalized criteria for treatment selection that would improve life expectancy compared with routine partial nephrectomy (PN) in patients with baseline chronic kidney disease (CKD). This extension of life expectancy was generally driven by patients spared from worsened CKD and associated mortality risks when these outweighed oncologic risks. Whereas all simulated patients with normal renal function were most effectively treated by using PN, patients with mild CKD experienced the greatest life expectancy from PN only when the degree of tumor anatomic complexity did not elevate the risk of renal functional decline after PN. In several simulated subgroups with moderate CKD, personalized treatment decisions extended life expectancy by more than 2 years compared with a standard surgical approach. To provide context, this degree of life expectancy benefit is comparable to highly effective interventions such as smoking cessation in young adult males (70).

Furthermore, our results support a potential role for MRI in decision making for patients with CKD because of the low probability of tumor progression for papillary RCC during active surveillance and the minimal oncologic benefit of treating all cancers detected by biopsy or all growing lesions that may be malignant or benign (17,71–73). The accuracy of MRI guidance in selecting papillary RCC reflects the literature, focusing on well-circumscribed cortical masses with T2-weighted hypointensity and low-level enhancement that generally represent type 1 papillary RCC (12,13,74). More central, ill-defined masses are predictive of papillary type 2 lesions, which are generally not considered candidates for active surveillance because of higher oncologic risks; stronger ability at imaging to discriminate between type 1 versus type 2 papillary RCC subtypes would further support the use of MRI for decision making (75,76). Biopsy-based treatment of all renal cancers benefited a limited subset of 65-year-old men and women with comorbidities (CCI \( \geq 1 \)) and mild CKD (stage 2) with moderate to high tumor anatomic complexity. However, an alternative use of biopsy for risk stratification, in which RCC histologic subtype guides therapy, was favorable over all other strategies in most patients with CKD stage 3 or comorbidities. A Surveillance, Epidemiology, and End Results Medicare analysis of initially untreated stage T1a RCC yielded differences in the 5-year metastatic rates among RCC subtypes, and therefore biopsy-based treatment of the more aggressive clear cell tumors acted as a more accurate alternative to MRI guidance for surveillance.

Modeling a patient’s candidacy for each management approach must account for uncertainty and parameter variability. The likelihood of benign histologic results, biopsy sensitivity, the rate of renal functional decline after ablation and PN, and the metastatic rate of untreated malignancies affected the preferred treatment strategy. As expected, higher metastatic disease rates (>2%) in untreated lesions favored initial treatment with PN for a larger range of CKD stage and NS. Meanwhile, when ablation was associated with the same local recurrence rate as PN
with all other assumptions held constant, patients with normal renal function were most effectively treated with ablation.

To our knowledge, previous decision-analytic studies for renal tumor treatment selection have not incorporated analysis of competing causes of mortality, including comorbidity status or renal functional harms, and to our knowledge the comparative effectiveness of selection methods for active surveillance has also not been assessed. Chang et al (77) and Pandharipande et al (78) previously modeled the cost effectiveness of percutaneous ablative therapy and also biopsy for small renal tumors, but they did not weigh oncologic versus nononcologic risks of comorbidity status and baseline CKD because the association with survival after PN has been more recently recognized. Active surveillance of stage T1a tumors has been associated with metastatic rates of 1%–2%, and large sample sizes required for small differences in oncologic and overall survival among alternative approaches are prohibitive for prospective trials. Our analysis may help to streamline clinical trial design, and serve as a shared decision-making tool for patients to comprehend risks and understand how their values and preferences might best align with the available options. The cost effectiveness of the use of our risk-stratifying method for decision making remains to be seen and requires a dedicated analysis.

Our study limitations included the strength of evidence available for some of the model parameters, such as the lack of long-term (ie, >10 years) prospective outcomes data for ablation and active surveillance regarding cancer-specific survival. Recent prospective registry data (46) supported a 1%–2% rate of metastasis during surveillance within the first 2 years after lesion discovery. Longer term multi-institutional comparative data on renal functional preservation for moderate and high NS scores after renal mass ablation and PN would also further decrease uncertainty about tumor anatomy as a predictor of renal functional outcomes after each treatment. We hope our results will inform design of trials to compare nephron-sparing treatment with specific forms of active surveillance, and as further data become available our modeling assumptions can be updated. In the model, the highest NS was associated with higher risk of residual and recurrent tumor after percutaneous ablation, but in practice the central location of some lesions may simply preclude ablative therapy. As part of the inherent simplifications and assumptions of a modeling approach, we did not vary renal functional outcomes by the approach for PN (ie, open vs laparoscopic PN). Finally, some strategies for active surveillance were not explicitly tested in the model such as avoiding surgical resection of oncocytc neoplasms only (oncocytoma or chromophobe RCC) as shown on biopsy results or treatment on the basis of high- versus low-grade RCC, which is susceptible to sampling error.

In conclusion, life expectancy for patients with chronic kidney disease (CKD) and small renal tumors has potential for substantial improvement with personalized treatment selection, which explicitly accounts for competing risks of mortality. PN remains most effective among patients of any age.
Table 6: Most Effective Treatment Pathway for 65-Year-Old Men and Women with Biopsy-Based Management Including Treatment Based on Histologic Subtype

| Parameter | Nephrometry Score | Treatment Pathway | Change in Life Expectancy (d) |
|-----------|------------------|-------------------|-------------------------------|
|           |                  | CKD Stage 2       |                               |
|           |                  |                   | CKD Stage 3a                  |
|           |                  |                   | CKD Stage 3b                  |
| 65-year-old men |                  |                   |                               |
| CCI       |                  |                   |                               |
| 0         | 4–5              | PN > ABL          | 49                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 30                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 8                             |
| 0         | 6                | PN > ABL          | 28                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 63                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 9                             |
| 0         | 7                | MRI > ABL         | 30                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 27                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 8                             |
| 0         | 8–9              | MRI > ABL         | 12                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 23                            |
|           |                  |                   | MRI > CC                     |
|           |                  |                   | 8                             |
| 0         | 10               | CC > MRI          | 15                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 69                            |
|           |                  |                   | MRI > CC                     |
|           |                  |                   | 26                            |
| ≥1        | 4–5              | PN > ABL          | 10                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 10                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 8                             |
| ≥1        | 6                | PN > ABL          | 12                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 8                             |
|           |                  |                   | CC > MRI                     |
| ≥1        | 7                | CC > MRI          | 20                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 24                            |
|           |                  |                   | (CC = MRI) > 25               |
|           |                  |                   | WW                           |
| ≥1        | 8–9              | CC > MRI          | 22                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 16                            |
|           |                  |                   | (CC = MRI) > 26               |
|           |                  |                   | WW                           |
| ≥1        | 10               | CC > MRI          | 35                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 8                             |
|           |                  |                   | MRI > CC                     |
| 65-year-old women |                  |                   |                               |
| CCI       |                  |                   |                               |
| 0         | 4–5              | PN > ABL          | 54                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 46                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 8                             |
| 0         | 6                | PN > ABL          | 42                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 64                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 9                             |
| 0         | 7                | MRI > ABL         | 51                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 27                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 9                             |
| 0         | 8–9              | CC > MRI          | 28                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 25                            |
|           |                  |                   | MRI > CC                     |
|           |                  |                   | 8                             |
| 0         | 10               | CC > MRI          | 44                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 58                            |
|           |                  |                   | MRI > CC                     |
|           |                  |                   | 10                            |
| ≥1        | 4–5              | PN > ABL          | 12                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 15                            |
|           |                  |                   | CC > MRI                     |
| ≥1        | 6                | PN > ABL          | 10                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 16                            |
|           |                  |                   | CC > MRI                     |
| ≥1        | 7                | CC > MRI          | 33                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 26                            |
|           |                  |                   | (CC = MRI) > 40               |
|           |                  |                   | WW                           |
| ≥1        | 8                | CC > MRI          | 61                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 21                            |
|           |                  |                   | (CC = MRI) > 32               |
|           |                  |                   | WW                           |
| ≥1        | 10               | CC > MRI          | 68                            |
|           |                  |                   | CC > MRI                     |
|           |                  |                   | 10                            |
|           |                  |                   | MRI > CC                     |
|           |                  |                   | 15                            |

Note.—Minimal difference in life expectancy was determined by using criterion of 7 days or less difference between life expectancies of the treatment strategies. The greater-than symbol indicates the strategy resulted in greater than 7 days difference in life expectancy compared with the next most effective strategy. Strategies in parentheses indicate less than 7 days difference in life expectancy between the two strategies. ABL = percutaneous ablation, BX = biopsy-based treatment of cancers, CC = biopsy-based treatment of clear cell renal cell carcinoma, CCI = Charlson comorbidity index, CKD = chronic kidney disease, PN = partial nephrectomy, WW = watchful waiting (ie, surveillance with treatment of growing lesions).

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with normal renal function. Among patients with baseline CKD and small renal tumors, MRI has potential to non-invasively help stratify patients for oncologic risk, and may help to extend life expectancy compared with surveillance for growth or biopsy of all lesions. Biopsy-based management was superior only when RCC was treated according to histologic subtype as a more accurate form of subtyping and risk stratification in patients with CKD stage 3 or baseline comorbidities.

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