Cost-Effectiveness Analysis of Nephron Sparing Options for the Management of Small Renal Masses

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Purpose: A recent increase in the detection of contrast enhancing renal masses 4 cm or smaller suspicious for malignancy has led to the widespread use of nephron sparing options. Limited data exist to help clinicians decide which of these competing nephron sparing therapies is most appropriate. We performed a cost-effectiveness analysis to evaluate the relative clinical and economic merits of commonly available nephron sparing strategies for small renal masses.

Materials and Methods: We developed a decision analytic Markov model estimating the costs and health outcomes of treating a healthy 65-year-old patient with an asymptomatic unilateral small renal mass using competing nephron sparing options of immediate intervention (ie open and laparoscopic partial nephrectomy as well as laparoscopic and percutaneous ablation), active surveillance with possible delayed intervention and nonsurgical management with observation. Benefits were measured in quality adjusted life-years. We used a societal perspective, lifetime horizon and willingness to pay threshold of $50,000 per quality adjusted life-year gained. Model results were assessed with sensitivity analyses.

Results: In the base case scenario the least costly option was observation and the optimal option was immediate laparoscopic partial nephrectomy, which had an incremental cost-effectiveness ratio of $36,645 per quality adjusted life-year gained compared to surveillance with possible delayed percutaneous ablation. Results were sensitive to age at diagnosis, health status and tumor size.

Conclusions: Immediate laparoscopic partial nephrectomy is the preferred nephron sparing option for healthy patients younger than 74 years old with a small renal mass. Surveillance with possible delayed percutaneous ablation is a cost-effective alternative for patients with advanced age or significant comorbidities. Observation maximizes quality adjusted life-years in patients who are poor surgical candidates or with limited life expectancy (less than 3 years).

Key Words: kidney neoplasms, nephrectomy, ablation techniques, decision support techniques, cost-benefit analysis

Abbreviations and Acronyms

CC = complication and comorbidity

CEA = cost-effectiveness analysis

CKD = chronic kidney disease

ICER = incremental cost-effectiveness ratio

LPN = laparoscopic partial nephrectomy

LY = life-year

OPN = open partial nephrectomy

QALY = quality adjusted life-year

QOL = quality of life

SRM = small renal mass

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See Editorial on page 1560.

THE management of localized renal masses has evolved in the last 2 decades. Historically clinicians recommended routine radical nephrectomy for all masses confined to the kidney due to concerns for malignancy.[1] Recently the proliferation of contrast enhancing renal masses 4 cm or smaller

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suspicious for malignancy (ie SRMs)[2] has led clinicians to favor nephron sparing options that avoid the unnecessary removal of normal renal parenchyma.[3]

Numerous nephron sparing options have gained acceptance for managing SRMs. Open and laparoscopic partial nephrectomy result in disease-free and cancer specific survival rates comparable to those of radical nephrectomy for patients with SRMs.[4] Meta-analyses report that laparoscopic and percutaneous ablation are also clinically effective therapies for SRMs.[5,6] Other investigators have proposed surveillance with delayed intervention[7] or observation without a plan for intervention[8] as reasonable options in particular clinical scenarios.

Despite evidence for the clinical effectiveness of nephron sparing options, limited comparative data exist to identify the most appropriate therapy for managing SRMs. Decision analytic modeling is a powerful tool that synthesizes evidence from multiple sources to estimate lifetime outcomes and explicitly evaluates the impact of uncertainty on those outcomes. CEA uses the results of decision analytic modeling to assess the relative merits of competing treatment options in the setting of limited resources. In the current study we performed a CEA to estimate the costs and benefits of commonly available nephron sparing options in the management of SRMs.

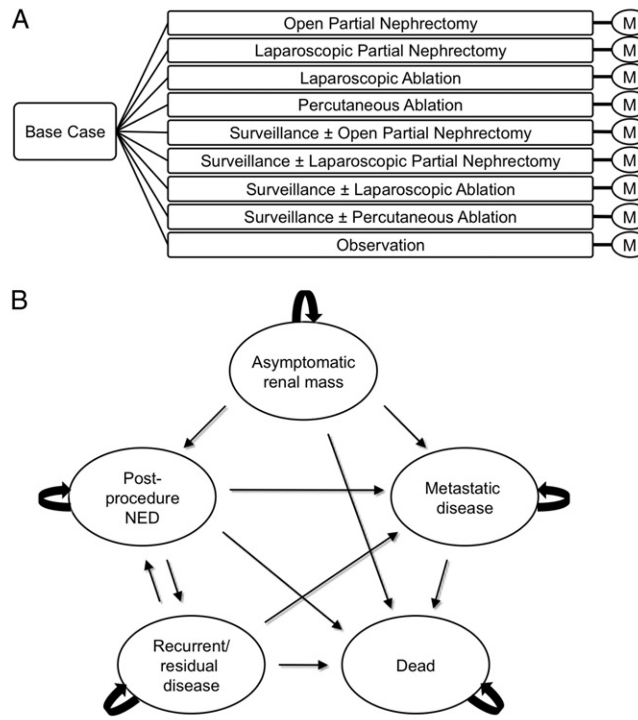

Figure 1. Decision analytic Markov model simulating management outcomes for 65-year-old healthy, asymptomatic patient with SRMs suspicious for malignancy (base case). *A*, decision tree with competing management strategies of immediate options (open and laparoscopic partial nephrectomy, and laparoscopic and percutaneous ablation), delayed options (surveillance possibly followed by intervention) and nonsurgical option (observation). *M*, Markov model. *B*, Markov model with 5 health states. Lifetime health outcomes and costs are determined by calculating cumulative time and expenses in each health state. *NED*, no evidence of disease.

METHODS

Model Design

We developed a Markov model with TreeAge Pro Suite 2009 (TreeAge Software, Inc., Williamstown, Massachusetts) to evaluate the competing nephron sparing strategies of 1) immediate options (ie surgical intervention without initial surveillance), 2) delayed options (ie initial surveillance with possible delayed surgical intervention) and 3) nonsurgical management (ie observation with no plan for surgical intervention). In total we compared 9 different strategies (fig. 1, *A*). We grouped cryoablation and radio frequency ablation together as ablative therapies based on their similar costs, QOL decrement and clinical efficacy.[5,6] Given the limited adoption of LPN in the medical community,[9] a secondary analysis excluded the option of LPN to represent the situation at some centers.

The model determined the outcomes using a 3-month cycle length, societal perspective and lifetime horizon (fig. 1, *B*). All benefits and costs were discounted at 3% per year. We ranked the nephron sparing options in ascending order of average discounted lifetime costs, and eliminated any strategy that was more costly and less effective than another option or combination of other options (ie dominated strategies). Benefits were measured in LYs and QALYs, and costs were reported in 2008 U.S. dollars. An ICER for each strategy on the efficiency frontier was calculated by comparing the strategy to the next best alternative using LYs gained and QALYs gained as described by the Panel on Cost-effectiveness in Health and Medicine.[10]

Base Case

The base case was an asymptomatic, healthy 65-year-old patient with an incidentally found, unilateral SRM amenable to all commonly available nephron sparing options. The base case patient had normal renal function and an unremarkable contralateral kidney.

Key Assumptions

We assumed that 25% of SRMs were benign,[11] and that benign and malignant tumors could not be distinguished based on growth rate.[12] For delayed options indications for intervention following surveillance included interval tumor growth or patient choice.[13,14] Renal tumors that had grown beyond 4 cm while on surveillance were managed with laparoscopic radical nephrectomy. Otherwise the planned delayed intervention was performed. A 4 cm cutoff was selected for OPN and LPN because we assumed this generally reflects the common clinical scenario at most medical centers. Because percutaneous biopsy performed in advance of the treatment to guide therapeutic decision making is currently not uniformly practiced,[15] we

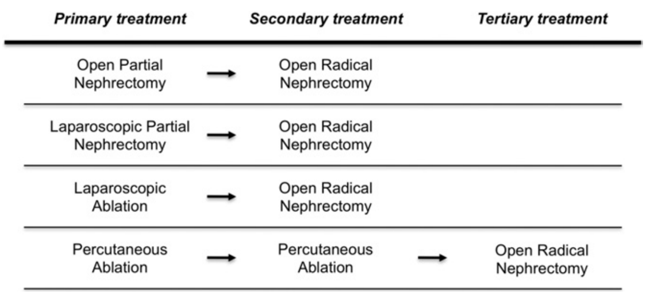

Figure 2. Re-treatment protocol for secondary and tertiary treatment following detection of local recurrent/residual disease after primary treatment.

assumed no pretreatment renal biopsy to evaluate for malignancy.

Following surgical therapy the detection of residual or recurrent tumors led to possible additional procedures (fig. 2). We assumed a unique rate of new onset postoperative CKD for each intervention associated with a reduction in QOL, increase in baseline health expenditures and increase in age adjusted mortality.

For patients in whom metastatic disease developed we modeled sunitinib as first line therapy and sorafenib (50%) or everolimus (50%) as second line therapy. Patients with further disease progression received best supportive care and 1 week of hospice care for 10%. We assumed a negligible risk for computerized tomography induced malignancy given the older age of our base case.[16]

Model Inputs

Due to the paucity of prospective, randomized controlled trials assessing nephron sparing procedures, model parameters were primarily derived from retrospective studies, with preference given to population based studies, multi-institutional studies and meta-analyses. The parameters were calibrated incorporating the assumptions as previously described (model calibration details described elsewhere).

We used baseline age specific QOL estimates from the Medical Expenditure Panel Survey.[17] Each surgical intervention was associated with a QOL reduction, which resolved by 3 months after intervention (table 1). Age specific baseline health costs were estimated from national averages[18,19] in addition to treatment, complication and followup costs for each nephron sparing option. Minor or major perioperative complications were associated with increased costs based on Medicare Severity-Diagnosis Related Group codes for CC as well as major CC code, respectively, as defined by the Centers for Medicare and Medicaid Services. We estimated the indirect costs of recovery from Centers for Medicare and Medicaid Services reimbursement for home health care following each intervention.

Sensitivity Analysis

The robustness of the results was tested with extensive 1-way and multi-way sensitivity analyses. We also considered alternative patient and tumor characteristics with sensitivity analyses.

RESULTS

Base Case Results

Observation was the lowest cost and least effective nephron sparing option, accruing an average lifetime discounted cost of $82,213 and 8.91 QALYs (table 2). The next nondominated strategy was surveillance with possible delayed percutaneous ablation, generating an ICER of $33,604/QALY gained compared to observation (fig. 3). The optimal strategy for our base case was immediate LPN with an average discounted cost of $114,515 and 9.82 QALYs yielding an ICER of $36,645/QALY gained. All other strategies were eliminated by extended or strict dominance. Secondary analysis without the option for LPN revealed that immedi-

Table 1. *Key model inputs for the base case analysis*

						Metastatic Disease		
	OPN	LPN	Laparoscopic Ablation	Percutaneous Ablation	Surveillance/ Observation	First Line Therapy With Sunitinib	Second Line Composite Therapy	Best Supportive Care
QOL adjustment*	0.7	0.88	0.9	0.96	0.97	0.73	0.7	0.55
Total cost of intervention:†								
No CC	$17,122	$13,335	$11,848	$ 3,778	—			
CC	$19,777	$15,990	$14,504	$11,643	—			
Major CC	$27,860	$24,073	$22,587	$19,726	—			
3-Mo probabilities (%):‡								
Recurrent/residual disease	0.13	0.17	2.97	4.47	—			
Metastatic disease	0.19	0.19	0.44	0.5	0.69			
3-Mo costs for systemic therapy						$11,693	$14,446	$33,634
3-Mo probability for disease progression (%)‡						16.5	36	90§

* Relative to the age adjusted baseline QOL.
† Includes direct and indirect costs.
‡ Probabilities derived from $p = 1 - e^{-rt}$ (transition probabilities [p], hazard rate [r] and time period [t]). The probabilities for recurrent/residual disease following ablation are based on a nonconstant rate and the initial 3-month probabilities are listed.
§ Equivalent to probability of mortality.

Table 2. *Base case results*

	Total Cost	Total LYs	Total QALYs	Analysis With All Management Strategies Available		Analysis Without LPN	
				ICER ($/LY gained)	ICER ($/QALY gained)	ICER ($/LY gained)	ICER ($/QALY gained)
Observation	$82,213	11.689	8.91	—	—	—	—
Surveillance ± percutaneous ablation	$95,950	12.081	9.32	Dominated	$33,604	Dominated	$33,604
Immediate percutaneous ablation	$103,629	12.177	9.39	Dominated	Dominated	Dominated	Dominated
Surveillance ± laparoscopic ablation	$104,950	12.183	9.36	Dominated	Dominated	Dominated	Dominated
Surveillance ± LPN	$106,614	12.536	9.59	Dominated	Dominated	—	—
Surveillance ± OPN	$108,935	12.538	9.57	Dominated	Dominated	Dominated	Dominated
Immediate LPN	$114,515	12.837	9.82	$28,148	$36,645	—	—
Immediate OPN	$117,234	12.841	9.8	$646,405	Dominated	$30,406	$44,372
Immediate laparoscopic ablation	$117,380	12.335	9.44	Dominated	Dominated	Dominated	Dominated

ate OPN was the optimal management strategy with an average lifetime discounted cost of $117,234 and 9.8 QALYs resulting in an ICER of $44,372/QALY gained.

Using pairwise comparisons of immediate vs delayed options we found that delayed options were consistently less costly and less effective than their immediate option counterparts (table 3). In the base case scenario we estimated that nearly 90% of patients on a delayed option strategy ultimately underwent intervention. The period of surveillance spared 5.4% of patients with benign SRMs from unnecessary therapy. Surveillance also translated into a 7.25% increase in the number of patients with metastatic disease attributable to the absence or delay in therapy. While on surveillance 0.6% of SRMs grew beyond 4 cm in size and missing this

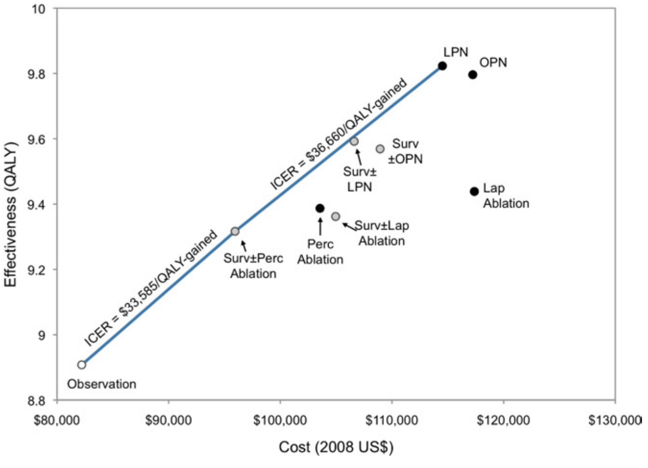

Figure 3. CEA of competing nephron sparing management strategies for healthy, asymptomatic 65-year-old patient with SRM suspicious for malignancy. Preferred strategies were observation, surveillance (*Surv*) with possible delayed percutaneous (*Perc*) ablation and immediate laparoscopic (*Lap*) partial nephrectomy. Based on willingness to pay threshold of $50,000/QALY, optimal strategy was immediate LPN with ICER of $36,660/QALY gained.

window of opportunity for a nephron sparing option resulted in a 2.5% increase in patients with postoperative CKD. Compared to their delayed option counterparts, immediate extirpative options (ie OPN and LPN) had an ICER of less than $50,000/QALY gained while immediate ablative options had an ICER greater than $50,000/QALY gained (table 3).

Sensitivity Analysis

Immediate LPN was the optimal treatment strategy for the base case across a wide range of probabilities for complications, postoperative QOL adjustments and recurrence rates. It remained the optimal nephron sparing option only if the indirect cost of convalescence was less than $5,750 and the 3-month metastatic disease probability less than 0.0015 (0.15%). If these criteria were not met, immediate OPN represented the preferred management strategy for the base case.

The main expenditures associated with observation were periodic imaging studies. Despite widely varying costs of imaging studies the average discounted cost of observation remained consistently at least $10,000 less than other treatments. Observation was the preferred nephron sparing option if the 3-month probability of metastatic disease decreased to less than 0.005 (0.5%). Otherwise base case results were stable across a range of QOL values and costs.

Compared to extirpative options, the costs and health outcomes for ablative therapies were disproportionately influenced by posttreatment events. The average discounted costs increased by as much as $5,000 following ablative therapy due to unnecessary postoperative surveillance of patients with benign SRMs, and nearly $10,000 for secondary and tertiary therapies to treat patients with recurrent or residual disease. Ablative therapies were also associated with higher probabilities of progression to metastatic disease.

Table 3. *Pairwise comparisons between immediate and delayed approaches*

	Total Cost	Total LY	Total QALY	ICER ($/LY gained)	ICER ($/QALY gained)
LPN:					
Delayed	$106,614	12.536	9.59	—	—
Immediate	$114,515	12.837	9.82	$26,206	$34,197
OPN:					
Delayed	$108,936	12.538	9.57	—	—
Immediate	$117,234	12.841	9.80	$27,408	$36,507
Laparoscopic ablation:					
Delayed	$104,951	12.183	9.36	—	—
Immediate	$117,380	12.335	9.44	$81,757	$162,221
Percutaneous ablation:					
Delayed	$95,942	12.081	9.32	—	—
Immediate	$103,550	12.177	9.39	$79,223	$107,957

Alternative Clinical Scenarios

Our findings were sensitive to patient and tumor characteristics. In the base case immediate LPN was the optimal strategy for healthy patients (ie low perioperative mortality risk) younger than 74 years old. This upper age limit for LPN varied with tumor size, at 65 years old for tumors less than 2 cm in size to 75 years old for tumors 3 to 4 cm in size (fig. 4). Surveillance with possible delayed percutaneous cryoablation was the most economically efficient strategy for patients who were older and/or had medical comorbidities (ie increased perioperative mortality risk). For poor surgical candidates and patients with limited life expectancy (less than 3 years) observation was the preferred alternative management strategy.

DISCUSSION

In 2009 an estimated 57,000 renal tumors were diagnosed in the United States resulting in more than $4.4 billion in health care expenditures.[20,21] With 48% to 66% of these newly identified renal tumors measuring 4 cm or smaller there were more than 25,000 SRMs amenable to nephron sparing treatment options.[3] Because the economic burden of SRMs is substantial and growing, it is important to understand the clinical and economic consequences of the available nephron sparing treatments for SRMs.

Our analysis reveals that immediate LPN is the preferred nephron sparing option for healthy 65-year-old patients who present with an asymptomatic, unilateral SRM concerning for malignancy. If LPN is not an available option, immediate treatment with OPN becomes the optimal strategy. However, the most economically efficient management strategy depends on the clinical scenario (fig. 4). Immediate extirpative strategies represent the optimal nephron sparing option for healthy, younger patients. Surveillance with possible delayed percutaneous ablation is preferred for less healthy and older patients. Observation represents the best strategy for patients who are poor surgical candidates and who have a life expectancy of less than 3 years. Laparoscopic ablation was not preferred in any scenario.

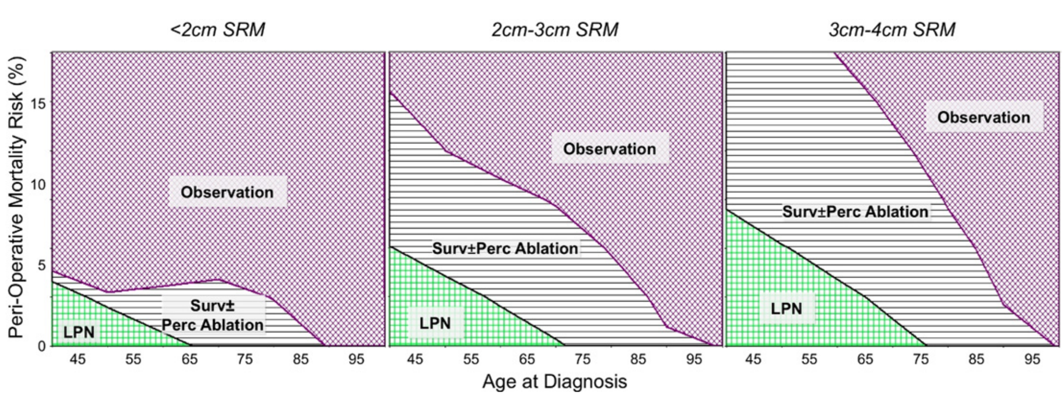

Figure 4. Optimal nephron sparing management strategy for SRM under alternate clinical scenarios. Multi-way sensitivity analysis varied parameters for age, health status (risk of perioperative mortality) and tumor size. Willingness to pay threshold for analysis was $50,000/QALY. *Surv*, surveillance. *Perc*, percutaneous.

Our results are driven by the lower rates of metastatic disease with extirpative options compared to ablative options or observation. For the base case, systemic treatment of metastatic disease with targeted therapeutic agents (eg sunitinib, sorafenib, everolimus) is associated with the largest average discounted direct cost ($73,000) and the largest decrease in QOL (0.67) of any health state in our model. Not surprisingly, previous economic evaluations report that the use of targeted therapy for the management of metastatic renal cell carcinoma is not cost-effective at a willingness to pay threshold of $50,000/QALY gained.[22]

Furthermore, extirpative options have cost savings compared to ablative therapies because of the ability to pathologically confirm the presence of benign tumors. After partial nephrectomy the 25% of patients determined to have benign tumors were spared substantial followup costs and the anxiety about recurrent disease. In contrast, after ablative therapy these patients unnecessarily accrue this cost and decreased in QOL. This advantage for extirpative therapies is disproportionately larger among younger patients because the costs of postoperative surveillance accumulate over time. Therefore, partial nephrectomy strategies are preferentially favored in younger patients, even among those who are less healthy (fig. 4).

The potential benefits of ablative therapies are reduced in part by the higher probability of repeat procedures. Our model estimated that ultimately recurrent or residual disease develops in nearly 20% of patients following ablation, which is consistent with published results.[23] These patients not only experience a reduction in QOL but also accumulate substantial costs from the additional therapy. Nevertheless, percutaneous ablation was associated with the lowest perioperative complication and mortality rates, thus making it favored in older and less healthy patients (fig. 4).

Delayed options are consistently less costly but also less effective than their immediate option counterparts (table 3). Active surveillance is appropriate only for older and less healthy patients who plan on undergoing delayed ablative therapy rather than partial nephrectomy. Among these patients the benefits of avoiding unnecessary surgery when SRMs are benign or indolent outweigh the slightly increased risk of postoperative CKD and progression to metastatic disease. Conversely patients considering OPN or LPN strategies should proceed to therapy without initial surveillance. For extirpative therapies surveillance conveys fewer benefits because patients with benign SRMs are identified through histopathological evaluation of the specimen. Observation represents the best strategy for patients who are poor surgical candidates and those who have a limited life span because they will not tolerate interventions well and have significant competing risk factors for mortality in addition to their SRM.[24]

Our findings differ from those of a prior analysis by Pandharipande et al, in which the authors concluded that percutaneous RFA is preferred compared to OPN.[25] The difference is partly due to our use of more recent model inputs and the recommended societal perspective.[26] The prior study assumed complete tumor ablation after 2 percutaneous treatments. In contrast, based on studies published since their analysis, we modeled an 8% short-term incidence of local tumor recurrence after 2 percutaneous ablative procedures,[5] and incorporated salvage radical nephrectomy[27] and the associated consequences of postoperative CKD.[28] Additionally, Pandharipande et al did not include the substantial costs of perioperative complications in their analysis.[25] Although uncomplicated percutaneous procedures are the least costly options ($3,778), minor or major complications increase procedural costs to $11,643 or $19,726, respectively, which approach the costs of extirpative treatments (table 1). Finally, Pandharipande et al did not consider the cost savings of identifying benign tumors with partial nephrectomy or the expenditures of metastatic disease, which are substantial with the widespread use of targeted therapy.

Our identification of immediate LPN as the most effective and cost-efficient strategy to treat healthy patients with SRMs raises concerns as this laparoscopic procedure has had limited adoption by clinicians.[9] If LPN is unavailable, then immediate OPN is the most cost-effective nephron sparing alternative in younger, healthier patients. The recent introduction of robotic technology may reduce the steep learning curve of LPN. However, the additional costs associated with robot-assisted procedures may outweigh the benefits. An economic evaluation of robot-assisted partial nephrectomy is warranted.

In terms of limitations our model relies primarily on data from retrospective studies and assumptions by clinical experts, which are both subject to bias. Moreover we derived long-term probabilities by calculating rates from short and intermediate term studies.[29] These rates may change over time, resulting in inaccurate long-term estimates. Although we calibrated and validated the model according to published data, used discounting that decreases the influence of uncertain long-term estimates and performed extensive sensitivity analyses testing uncertainties, our assumptions and choices about imputed values may be imperfect, thereby potentially decreasing model validity.

CONCLUSIONS

The current study presents clinical recommendations for the management of a newly diagnosed contrast enhancing SRM suspicious for cancer. The analysis finds that healthy 65-year-old patients should undergo immediate LPN. Moreover this strategy maximizes the expected QALYs and is cost-effective for healthy patients younger than 74 years old. If LPN is not available then immediate OPN is the most economically efficient alternative. However, for patients who have an increased risk of perioperative mortality, a plan for active surveillance with possible delayed percutaneous ablation is the preferred treatment strategy. Poor surgical candidates or patients with a life expectancy less than 3 years should select observation only.

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