Title page

A decision analysis evaluating screening for kidney cancer using focused renal ultrasound

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Running title: Decision analysis of screening for renal cancer

Key words: Cost-effectiveness, Renal cell cancer, RCC, kidney cancer, Screening, Ultrasound

Funding: The Urology Foundation (SHR). Kidney Cancer UK (SHR and GDS). Renal Cancer Research Fund (SHR and GDS). CRUK Prevention Fellowship (C55650/A21464) (JUS). The funding sources had no role in data collection and analysis, nor the manuscript itself.

Financial Disclosure: PN has received consultancy fees from BMS, EUSA, Ipsen, MSD, Merck, Pfizer, Novartis. SDA has received honoraria from Pfizer and fees as medical advisor for Elypta AB. AB has received educational grants from Pfizer; consultancy fees from Pfizer, Roche, Novartis, BMS and EISAI. GDS has received educational grants from Pfizer, AstraZeneca and Intuitive Surgical; consultancy fees from Pfizer, Merck, EUSA Pharma and Cambridge Medical Robotics; Travel expenses from Pfizer and Speaker fees from Pfizer. All other authors have no financial disclosures.

Registration: Not applicable

Ethics: Health economics study not involving human participants therefore ethics approval not required.

Acknowledgements: We would like to thank Professors Simon Griffin and Vicky Goh, as well as Ms Christy Watson, our patient representative, for their input and advice. We would also

like to thank Kidney Cancer UK, The Renal Cancer Research Fund and The Urology Foundation for their support.

Abstract word count: 300/300

Manuscript word count: 2693/2500

Structured abstract

Background: Screening for renal cell carcinoma (RCC) has been identified as a key research priority; however, no randomised control trials have been performed. Value of information analysis can determine whether further research on this topic is of value.

Objectives: To determine (a) whether current evidence suggests screening is potentially cost-effective. If so, (b) in which age/sex groups, (c) identify evidence gaps and (d) estimate the value of further research to close those gaps.

Design, Setting, Participants: A decision model was developed evaluating screening in asymptomatic individuals in the UK. A National Health Service perspective was adopted.

Intervention: A single focused renal ultrasound scan compared with standard of care (no screening).

Outcome measures: Expected lifetime costs, quality adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER), discounted at 3.5%/annum.

Results: Given a prevalence of RCC of 0.34% (0.18-0.54%), screening 60 year-old men resulted in an ICER of £18,092/QALY[€22,843/QALY]. Given a prevalence of RCC of 0.16% (0.08-0.25%), screening 60-year-old women resulted in an ICER of £37,327/QALY[€47,129/QALY]. In the one-way sensitivity analysis, the ICER was <£30,000/QALY so long as the prevalence of RCC was ≥0.25% for men and ≥0.2% for women

at age 60 years. Given a willingness to pay threshold of £30,000/QALY[€37,878/QALY], the population expected value of perfect information was £194 million[€244 million] and £97 million[€123 million] for 60-year-old men and women respectively. The expected value of perfect parameter information suggests the prevalence of RCC and stage shift associated with screening are key research priorities.

Conclusion: Current evidence suggests one-off screening of 60-year old men is potentially cost-effective and that further research into this topic would be of value to society.

Patient Summary: Economic modelling suggests that screening 60-year-old men for kidney cancer using ultrasound may be a good use of resources and that further research on this topic should be performed.

Word count: 300/300

Introduction

Cost-effectiveness analyses (CEA) are classically performed to aid decisions regarding the value of implementing new interventions into a health service. More recently, value of information analyses (VOI) of screening interventions have been undertaken using the currently available evidence, prior to a large trial being undertaken, aiming to determine the value of investing future funds into further research[1]. Indeed, VOI has been used to examine uncertainty surrounding the optimal screening strategy for colorectal cancer and therefore prioritise future research efforts[2].

Screening for renal cell carcinoma (RCC) has repeatedly been identified as a research priority[3-6]. Over a quarter of individuals diagnosed with RCC have metastases at presentation. Five-year age standardized relative survival for these individuals is 6% compared to 84% for those with stage I disease[7]. Ultrasound has been proposed as a screening tool, as it is well tolerated, inexpensive and widely available[8]. National abdominal aortic aneurysm (AAA) screening programs for 65-year-old men are established in the UK and Sweden and have demonstrated that an ultrasound-based screening program can be delivered in the community by trained technicians[9, 10]. Observational studies evaluating screening for RCC using ultrasound have been conducted. However, none were randomised, and all were published more than a decade ago[11-18]. Due to the relatively low prevalence of RCC in unselected asymptomatic individuals, a randomised controlled trial (RCT) sufficiently powered to detect an impact on survival would need to recruit hundreds of thousands of participants[11]. Therefore, we perform a decision analysis synthesizing the

currently available evidence, with the aim of determining the value of performing further research into this topic.

Methods

Scope of the decision model

A cohort simulation model was developed adopting a UK National Health Service perspective, consistent with Consolidated Health Economic Evaluation Reporting Standards (Supplement)[19, 20]. The model compares screening (intervention) versus the standard of care (no screening) in asymptomatic individuals from the general population. Screening consists of a single focused renal ultrasound, delivered by technicians in the community, similar to AAA screening[21]. If the ultrasound is reported as normal or as a simple cyst, the patient is discharged. Any other abnormality is investigated with an outpatient urology clinic ± CT as appropriate (Supplemental Figure 1). The primary outcomes are the incremental costs (2016 £GBP), incremental quality adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) comparing one-off screening with no screening. The ICER was defined as the mean incremental costs divided by the mean incremental QALYs. A cycle length of one year and a lifetime time horizon were adopted. Costs and QALYs were discounted at 3.5%/annum. The UK willingness to pay threshold of £20,000-£30,000/QALY gained [€25,252-€37,878/QALY] was used; therefore, an ICER>£30,000 was considered not to be cost-effective [19, 20].

Model structure

The model, which consisted of a decision tree with Markov models at each terminal node, was developed in Microsoft Excel (2016). The decision tree demonstrates the disease status (i.e. RCC, no RCC, benign incidental finding) and the test result (true positive/negative, false

positive/negative). Figure 1 represents a simplified schematic of the Markov models (Supplemental Figures 2-7).

Model inputs

Model inputs were derived through comprehensive literature reviews and where no data were available, through structured expert elicitation (Table 1) [8, 11, 22, 23]. Further details are available in the Supplemental Methods.

A meta-analysis demonstrated that the pooled prevalence of RCC detected by ultrasound was more than twice as high in studies from Europe and North America compared to Asia (0.17% (0.09-0.27%) *vs* 0.06 (0.03-0.09%)) (n=29,938)[11]. Only one study, by Mihara *et al*., reported the prevalence of RCC by age and sex, which screened Japanese individuals from 1983 to 1996 (overall prevalence of RCC: 0.09%)[14]. Although the study by Mihara *et al*. underestimates the true prevalence of RCC in a contemporary Western population, the relative prevalence by age and sex is likely to still be relevant[11, 14, 24]. Therefore, to derive likely prevalence rates in the UK by age and sex, the prevalence reported by Mihara *et al*. was used along with the results of the meta-analysis applied to the UK population reported by the Office for National Statistics (Table 1)[25].

The cost of AAA screening ultrasound in the UK is £37.53 [€47] [21]. In the base case, it was assumed screening renal ultrasound would have the same cost (Table 1). If ultrasound were to be performed by sonographers in secondary care, then it would be priced at £55 (IQR £38-£63) [€69], therefore this was evaluated in the sensitivity analysis[26].

No studies have evaluated the impact of screening for RCC on quality of life (QoL)[22]. Ultrasound screening for AAA and ovarian cancer was not associated with a disutility[27-31]. Therefore, ultrasound screening for RCC was assigned a disutility of 0 and this assumption was tested in the sensitivity analysis.

Model analysis

The decision model was run with 3000 Monte Carlo simulations as this achieved stability of results, defined as a coefficient of variation <2% for the SE of the incremental net monetary benefit[32]. In brief, this means a set of inputs was sampled from the respective distributions, the model calculated and repeated 3000 times to generate an empirical estimate of the uncertainty in cost-effectiveness. The ICER was evaluated for males and females aged 40, 50 and 60 years as estimates for prevalence of RCC were available for these groups based on the study by Mihara *et al*[14]. The population in whom screening is most cost-effective was determined from this and used as the base case for all subsequent analyses.

The expected value of perfect information (EVPI) and perfect parameter information (EVPPI) were determined. The EVPI summarises the value of eliminating all parameter uncertainty (i.e. perfect information), whereas the EVPPI summarises the value of eliminating individual parameter uncertainty[33, 34]. Thus, the EVPI provides an upper limit for all future research expenditure regarding the decision problem. The EVPPI determines the value of eliminating uncertainty in a parameter (or group of parameters), and so can be used to guide research

225 priorities[34]. The population VOI statistics were based on the number individuals eligible
226 for screening[35]. The EVPPI was determined by running the simulation 1000 times for the
227 inner loop and 2000 times for the outer loop. An approximation of the impact of screening
228 was obtained by multiplying the incremental cost and QALYs of screening (per patient) by
229 the number of individuals eligible for screening.
230
231

Results

Determining the most cost-effective screening population

The point estimate ICER is <£30,000/QALY for 50-year-old men and <£20,000/QALY for 60-year-old men (Table 2). The ICER is >£30,000/QALY for women of all ages, however the most favourable ICER is observed for 60-year-old women. Therefore, age 60 years (males and females) was chosen as the base case for all subsequent analyses.

Analysis of uncertainty

For 60-year-old males, there is a 62% probability that the ICER is <£20,000/QALY and a 66% probability that the ICER is <£30,000/QALY. For 60-year-old females, there is a 44% probability that the ICER is <£20,000/QALY and a 56% probability that the ICER is <£30,000/QALY (Supplemental Figure 8).

Sensitivity analyses

Cost-effectiveness improves as the prevalence increases and the cost of ultrasound decreases (Table 3). Using £37[€47] as the cost of ultrasound, the ICER remains <£30,000/QALY so long as the prevalence of RCC is ≥0.25% for men and ≥0.2% for women aged 60 years. Using our current estimates for the prevalence of RCC for 60-year-old women, the ICER is <£30,000/QALY if the cost of screening ultrasound was reduced from £37 to ≤£30[€47 to ≤€38].

For 60-year-old males, the ICER remains <£30,000/QALY so long as the disutility associated with screening is ≤0.05 for one week (Supplemental Table 6). The ICER is <£30,000/QALY, if the specificity of ultrasound is ≥85% (Supplemental Table 7). Furthermore, in the base case, it was assumed that the combined prevalence of incidental benign conditions detected by screening would be 2.7%[11, 17, 18]. The sensitivity analysis demonstrated that in 60-year-old men, the ICER remains <£30,000/QALY so long as the combined prevalence of other incidentally detected renal conditions is ≤20**%** (Supplemental Table 8). Sensitivity analyses for 60-year-old females are available in Supplemental Tables 6-8.

Value of information analysis

The number of individuals aged 60 years eligible to receive screening in the UK is 362,766 men/annum and 374,008 women/annum. Assuming a time horizon for which additional information is useful of ten years, this equates to a population that may benefit from screening of 3,122,576 men and 3,219,344 women (discounted at 3.5%)[36]. Given a willingness to pay threshold of £30,000/QALY, the population EVPI is £244,415,131 [€209,133,931] and £97,263,108 [€122,804,400] for 60-year-old males and females respectively (Supplemental Figure 9). The three parameters with the highest population EVPPI are the prevalence of RCC, the stage distribution of screen detected disease and the stage distribution of false negatives at screening (Figure 2).

Impact on health services

Compared with no screening, screening 60-year-old males results in an overall expected incremental cost per patient of £44.55 (cost of screening and treatment, discounted to present value) over a 30-year lifetime[€56]. The number of males eligible to receive screening in the UK is 362,766 per annum. Therefore, the present-value cost to the health service would be £16 million[€20 million] per cohort screened, over 30 years. However, the majority of screening costs are accrued up front when screening occurs. The expected incremental QALYs per patient is 0.0025 over 30 years (discounted to present value). Therefore, that equates to 893 QALYs gained per cohort screened. For 60-year-old women, screening would cost £17 million[€21 million] and would lead to 467 additional QALYs per cohort screened, over 30 years.

Discussion

Screening for RCC has the potential to improve survival outcomes[4, 5]. However, as with any screening program, there is also a potential for harm, including over-diagnosis, as well as psychological and economic implications for patients and society. No RCTs of screening for RCC have been undertaken[8]. We demonstrate that the population EVPI is £194 million and £97 million for 60-year-old men and women respectively. This suggests further research is likely to be of good value to the funder, and should be focused on estimating the prevalence of RCC and the stage shift associated with screening.

Determinants of cost-effectiveness

Using current evidence, this decision model suggests screening may be cost-effective in males but not females, due to lower prevalence of RCC in the latter[11, 14]. The true prevalence of RCC by age/sex in the UK is unknown. Sensitivity analysis suggests that screening may be cost-effective if the prevalence is ≥0.25% for males and ≥0.2% for females. A meta-analysis demonstrated the prevalence of RCC detected in middle-aged Americans undergoing screening CT is 0.21%[24]. Once again, the prevalence was not reported by age/sex, however it may indeed be above the threshold identified by our sensitivity analysis. Although beyond the scope of the present analysis, risk-stratified screening may increase cost-effectiveness by targeting screening towards individuals with a higher prevalence. At present there is a lack of specific, validated models to predict the risk of RCC and further research is required to elucidate this[8, 37]. Similarly, screening for AAA has been deemed cost-effective in men and not women, as the latter have a lower

prevalence of the disease[28, 38]. However, there are important equity considerations associated with screening only one sex[39].

The cost of screening ultrasound is a modifiable factor which is a major determinant of cost-effectiveness. Screening 60-year-old males remains cost-effective so long as the cost of ultrasound is <£60. This is very likely as it is below the current cost of ultrasound performed by a sonographer in secondary care[26]. When screening 60y females, the ICER drops <£30,000/QALY when the cost of ultrasound is reduced from £37 to £30. It is unclear whether the cost of technician-performed ultrasound may be reduced to this level. Renal ultrasound is technically more challenging to perform than aortic ultrasound. Accuracy is dependent on the size of the renal lesion and operator experience[40-42]. Our model suggests screening 60-year-old males remains cost-effective (i.e. ICER< £30,000) so long as the specificity of ultrasound is ≥85%, and the prevalence of benign incidental findings at ultrasound is ≤20%. All these conditions seem likely.

Potential harms of screening

Evidence on the impact of screening for RCC on QoL is lacking[8, 22]. In the base case, it was assumed that undergoing screening ultrasound was not associated with a disutility, and this may contribute to the results demonstrating that the EVPPI for utilities was £0. However, in the sensitivity analysis, we showed that for 60-year-old men if the disutility associated with screening renal ultrasound is ≥0.05 for one week, screening is no longer cost-effective. This is because a small reduction in utility would be applied to such a large number of individuals receiving screening that it would outweigh any benefit to the small minority of patients in

338 which RCC is detected. Therefore, it is essential that any future RCC screening studies
339 evaluate the impact of screening on QoL.
340
341 Strengths and limitations
342
343 A strength of this work is that it is the first decision analysis of screening for RCC in
344 asymptomatic individuals. The model was designed with input from a multidisciplinary team
345 of RCC experts and a patient advocate. Importantly, the model incorporates the impact of
346 incidental findings detected by screening on cost-effectiveness. Systematic reviews were
347 undertaken to determine key model inputs and where data were not available, structured
348 expert elicitation was performed[8, 11, 22, 23]. This ensures that uncertainty surrounding
349 parameter estimates was captured accurately, enabling reliable VOI[35].
350
351 The model represents a simplification of reality and shares some limitations inherent to all
352 CEAs. Due to structural assumptions within the model, it was not appropriate to assess the
353 impact of ultrasound sensitivity on the ICER, as the stage distribution of false positives was
354 determined by evidence from the literature. Some CEAs in other disease areas have
355 overcome this by modelling the natural history of undiagnosed disease[32]. However, there
356 are no existing data on the transition probabilities between undiagnosed RCC stages. As
357 there are eleven potential health states (diagnosed and undiagnosed stage I T1a, I T1b, II, III,
358 IV, death) this would require 20 transition probabilities to be derived through expert
359 elicitation. This would introduce undue uncertainty in the decision analysis, therefore it was
360 felt that the current structure was the most appropriate. High profile CEAs in other disease
361 areas, such as screening for breast cancer, have also chosen to develop less complex models

362 to minimize the assumptions and uncertainties arising from lack of data[43]. Life table
363 models and discrete event simulation models of screening for breast cancer have achieved
364 similar results[43, 44].
365
366 The CEA is limited by the absence of trial level data regarding certain model inputs.
367 Conversely, a major indication for the CEA was to determine if undertaking a trial of
368 screening was warranted on economic grounds. The prevalence of RCC was reported for a
369 limited number of age groups[11, 14]. It was not possible to evaluate repeated screening at
370 regular intervals, as screening studies scanned individuals only once. The model assumes
371 that cancer-specific mortality is determined by RCC stage and is the same in the screening
372 and no screening cohorts. Individuals with incidentally detected tumours have significantly
373 better survival compared to symptomatic patients, after adjusting for tumour grade and
374 stage[45]. Therefore, the model may underestimate the benefit of screening[46, 47].
375 However, as there are no RCTs demonstrating the effectiveness of screening, we do not
376 know if screening in a contemporary population would lead to a stage shift nor whether it
377 would impact survival. This consideration is particularly important as the number of
378 individuals undergoing abdominal imaging for other indications is rising[48]. Further trial
379 level data are required to quantify overdiagnosis and lead time bias. Additionally, there
380 were few data on the prevalence of benign incidental findings at screening, and their
381 associated impact on QoL or cost. We assigned a cost but no gain or loss of QALYs from
382 incidental findings. This simplification may underestimate the cost-effectiveness of
383 screening.
384

Conclusion

Given the available evidence and the current willingness to pay threshold, our model suggests that screening may be cost-effective in 60-year-old males. The prevalence of RCC by age/sex is a major determinant of cost-effectiveness and represents a key research priority, along with the stage shift associated with screening. Future work should focus on evaluating the potential harms of screening including the impact on QoL, incidental findings and overdiagnosis.

Figures

Figure 1: Structure of the Markov model

Figure 1 represents a simplified schematic of the Markov models; further details can be found in the Supplement. In brief, individuals without RCC can have a number of benign incidental findings (asymptomatic calculi, hydronephrosis etc). Individuals with RCC can be undiagnosed or diagnosed, by one of two ways: diagnosed via screening or opportunistically within the health service. Once RCC is diagnosed, individuals can be classified into one of the following five RCC health states: stage I T1a, stage I T1b, stage II, stage III and stage IV based on established AJCC staging criteria. Newly diagnosed (ND) health states are tunnel states reflecting costs and QALYs associated with the first year of diagnosis and treatment of RCC, with follow up costs accrued and discounted up front, as previously described [49]. These tunnel states will transition into long-term health states, which represent metastasis free (MF) states. Individuals will remain in each of these MF states until they progress (i.e. metastatic progression). Stage IV disease (shown in the dotted box) encompasses both newly diagnosed stage IV and metastatic recurrence. Stage IV disease may be subdivided into one of the following health states based on treatment: individuals with no progression (NP) on first line systemic therapy ("Stage IV, NP 1st line ST") and those with who do not receive systemic therapy ("Stage IV, no ST"). These can lead to no progression on second line therapy ("Stage IV, NP 2nd line ST"), no progression on third line therapy ("Stage IV, NP 3rd line ST"), or progressive disease ("Stage IV, PD"). All health states can lead to "non RCC death" (i.e. background mortality) or "RCC death" via the "Terminal" tunnel health state, representing costs associated with the final year of life [49]. Arrows to these death health states are not shown to maintain clarity in the diagram.

Figure 1

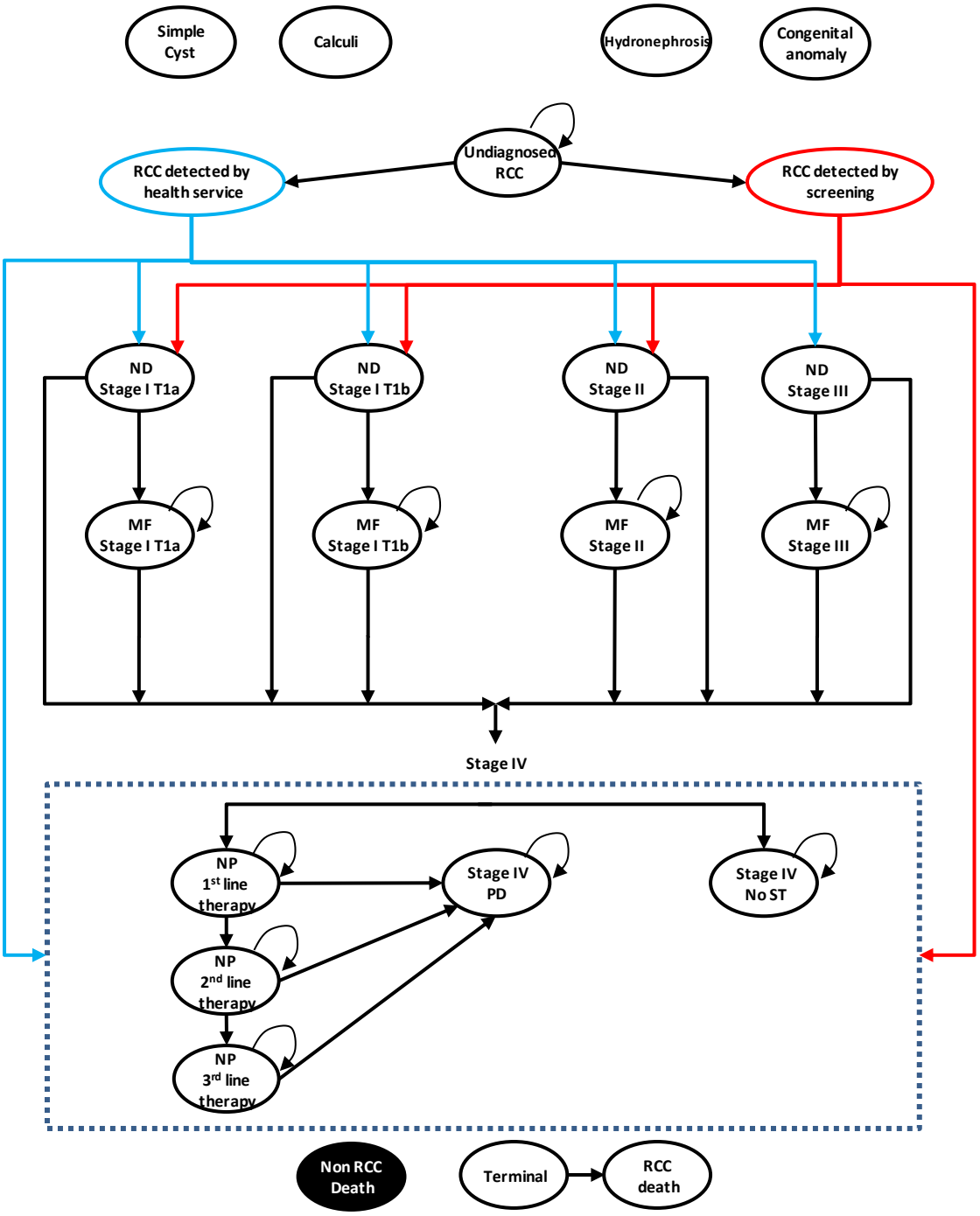
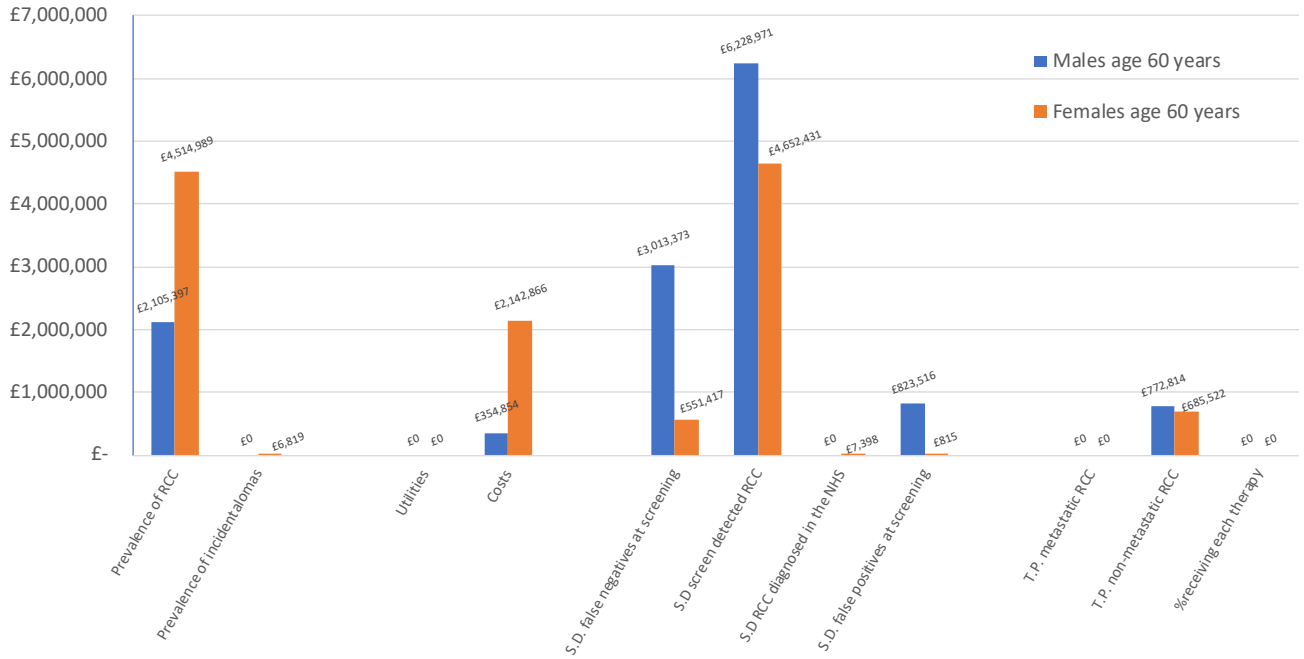

Simple Cyst
Calculi
Hydronephrosis
Congenital anomaly
Undiagnosed RCC
RCC detected by health service
RCC detected by screening
ND Stage I T1a
ND Stage I T1b
ND Stage II
ND Stage III
MF Stage I T1a
MF Stage I T1b
MF Stage II
MF Stage III
Stage IV
NP 1st line therapy
NP 2nd line therapy
NP 3rd line therapy
Stage IV PD
Stage IV No ST
Non RCC Death
Terminal
RCC death

Figure 2: Population expected value of perfect parameter information

The population expected value of perfect parameter information (EVPPI) at a willingness to pay threshold of £30,000/QALY is shown for males and females aged 60 years. The parameters investigated were: screening parameters, costs, utilities, transition probabilities (TP) and stage distribution (SD) i.e. the proportion of individuals with RCC in each cancer stage. The "% receiving each therapy" refers to the proportion of individuals with RCC who undergo each management option, for example, ablation, active surveillance, surgery (open vs laparoscopic, partial vs radical) etc. "Utilities" refers to all utilities in the model, not just the utility associated with screening. Note, the EVPPIs do not sum to the EVPI due to parameter correlation.



Tables

Table 1: Model inputs

For each model input, the mean estimate along with the 95% confidence interval (CI) or standard error (SE) is shown. For costs, the interquartile range (IQR) is reported as this is the data provided by the national schedule of referencing costs. Parameters of the distribution used in the probabilistic sensitivity analysis are demonstrated. For parameters derived through expert elicitation, the median estimate and 95% credibility intervals (CrI) are shown. For modified Connor Mosimann distributions (mCM), the a, b, L, U parameters are shown. Medians do not sum to 1, however means do (data not shown). The ordering of Zed parameters is critical to ensure correct calculation of probabilities, although this order may not be the same as the logical order (stages I-IV). Further details regarding how transition probabilities and summary costs were derived are available in the Supplement.

Parameter	Source	Mean (95% CI)	Distribution
Screening parameters			
Sensitivity of ultrasound	[16, 17, 50, 51]	81.8% (52.3%-94.9%)	Beta (9,2)
Specificity of ultrasound	[16, 17]	98.2% (97.9%-98.5%)	Beta (9771, 177)
Specificity of CT following a positive ultrasound	[17]	98.9% (96.0%-99.7%)	Beta (175,2)
Prevalence of asymptomatic hydronephrosis	[11]	0.48% (0.21-0.87%)	Beta (8.05, 1654.60)
Prevalence of asymptomatic stones	[11]	1.82% (0.59-3.64%)	Beta (5.03, 275.51)
Prevalence of other benign asymptomatic findings on screening~	[17, 18]	0.40% (0.30%-0.55%)	Beta (40, 9919)
Prevalence of RCC			
Prevalence in 40-year-old males	Adapted from [11, 14, 25]	0.14% (0.08-0.23%)	Beta (14.24, 9780.69)
Prevalence in 50-year-old males		0.23% (0.12-0.37%)	Beta (12.58, 5502.85)
Prevalence in 60-year-old males		0.34% (0.18-0.54%)	Beta (13.17, 3905.89)
Prevalence in 40-year-old females		0.07% (0.04-0.11%)	Beta (15.49, 21892.72)
Prevalence in 50-year-old females		0.09% (0.05-0.14%)	Beta (14.97, 16729.45)
Prevalence in 60-year-old females		0.16% (0.08-0.25%)	Beta (12.30, 8011.51)
Stage distribution			
Parameter	Source	Mean (95% CI or 95% CrI)	Distribution

Screen detected RCC			
Stage I T1a	[11]	45.45% (34.0%-57.4%)*	
Stage I T1b	[11]	40.91% (29.9%-53.0%)*	Dirichlet (30, 27, 9)
Stage II	[11]	13.64% (7.3%-23.9%)*	
	[11]		
Stages I-II	[11]	84.39% (78.8%-88.7%)	Dirichlet (173, 28 ,4)
Stage III	[11]	13.66% (9.6%-19.0%)	
Stage IV	[11]	1.95% (0.8%-4.9%)	
RCC detected by the health service			
Stage I T1a	[52]	55.58% (54.12%-57.0%)#	Beta (2511, 2007)
Stage I T1b	[52]	44.42% (43.0%-45.9%) #	Beta (2007,2511)
Stage I	[53]	44.21% (42.96%-45.46%)	Dirichlet (2678,578,1116,1686)
Stages II	[53]	9.54% (8.83%-10.31%)	
Stage III	[53]	18.42% (17.47%-19.42%)	
Stage IV	[53]	27.83% (26.72%-28.97%)	
Stage distribution of false positives			
Stage I T1a	[54-56]	60.7% (57.1%-64.1%)	Dirichlet (451, 168, 124)
Stage I T1b	[54-56]	22.6% (19.7%-25.8%)	
Stages II	[54-56]	16.7% (14.2%-19.5%)	
Stage III	[54-56]	0%	
Stage IV	[54-56]	0%	
False negatives at screening			
Stage I T1a	Structured expert elicitation [23]	76% (43%-95%)	mCM (6.72, 2.41, 0, 1)
Stage I T1b		9% (1%-44%)	mCM (0.35, 0.49, 0.157, 1)
Stage IV		4% (0-32%)	mCM (0.64, 0.40, 0, 1)
Stage II		1% (0%-14%)	mCM (10, 10, 0, 1)
Stage III		1% (0%-14%)	mCM (-)
Annual transition probabilities			
Parameter	Source	Mean (95% CI)	Distribution
Stage I T1a			
Stage I T1a > Stage I T1a		1-sum of other probabilities	
Stage I T1a > Stage IV	[57]	0.0110 (0.00552, 0.0183)	Beta (11.04, 991.96)
Stage I T1a > RCC death	[58]	0.00424 (0.00346,0.00509)	Beta (102.80, 24165.20)
Stage I T1b			
Stage I T1b > Stage I T1b		1-sum of other probabilities	
Stage I T1b > Stage IV	[57]	0.0326 (0.0216-0.0457)	Beta (26.91, 799.11)
Stage I T1b > RCC death	[58]	0.0198 (0.0178-0.0219)	Beta (349.31, 17322.70)
Stage II			
Stage II > Stage II		1-sum of other probabilities	
Stage II > Stage IV	[57]	0.0538 (0.0371, 0.0733)	Beta (31.85, 560.15)
Stage II > RCC death	[7]	0.0306 (0.0131-0.0544)**	Beta (7.86, 250.99)
Stage III			
Stage III > Stage III		1-sum of other probabilities	
Stage III > Stage IV	[57]	0.104 (0.0810,0.129)	Beta (64.69, 559.31)
Stage III > RCC death	[7]	0.105 (0.0828-0.131)**	Beta (64.88, 547.54)

No progression (NP) on 1st line therapy			
NP on 1st line therapy> NP on 1st line therapy	[59]	0.274 (0.242-0.307)	Dirichlet (201, 181, 351)
NP on 1st line therapy> progressive disease	[59]	0.247 (0.216-0.278)	
NP on 1st line therapy> death$	[59]	0.479 (0.443-0.515)	
No progression (NP) on 2nd line therapy			
NP on 2nd line therapy> NP on 2nd line therapy	[60]	0.186 (0.162- 0.211)	Beta (177.04, 775.96)
NP on 1st line therapy> progressive disease		1-sum of other probabilities	
NP on 1st line therapy> death$	[61]	0.595 (0.577-0.613)	Beta (1739.46, 1182.54)
No progression (NP) on 3rd line therapy			
NP on 3rd line therapy> NP on 3rd line therapy		1-sum of other probabilities	
NP on 3rd line therapy> progressive disease	[62, 63]	0.451 (0.420-0.482)	Beta (447.56, 545.44)
NP on 3rd line therapy> death$	[62, 63]	0.489 (0.458-0.520)	Beta (485.27, 507.73)
Stage IV, No systemic therapy			
No systemic therapy> No systemic therapy		1-sum of other probabilities	
No systemic therapy > death$	[64]	0.646 (0.616-0.677)	Beta (605.07, 330.93)
Progressive Disease (PD)			
PD>PD		1-sum of other probabilities	
PD> death$	[65]	0.908 (0.797-0.977)	Beta (33.58, 3.42)
Undiagnosed> Diagnosed RCC Opportunistic detection by health service	Structured Expert elicitation [23]	0.25 (0.01-0.76)	Beta (1.07, 2.65)
Proportion undergoing each management option			
Management option	Source	Proportion (n/N)	Distribution
Stage I RCC (T1a)			
Active Surveillance	Expert opinion	Age Dependent	Dirichlet (235, 223, 494, 52, 588, 25)
Percutaneous ablation	[66]	0.024 (77/3158)	Beta (77, 3081)
Open partial nephrectomy	[67]	0.145 (235/1617)	
Laparoscopic partial nephrectomy	[67]	0.138 (223/1617)	
Robotic partial nephrectomy	[67]	0.306 (494/1617)	
Open radical nephrectomy	[67]	0.032 (52/1617)	
Laparoscopic radical nephrectomy	[67]	0.364 (588/1617)	
Robotic radical nephrectomy	[67]	0.015 (25/1617)	
Stage I RCC (T1b)			
Open partial nephrectomy	[67]	0.074 (108/1455)	Dirichlet (108, 21, 81, 151, 1040, 54)
Laparoscopic partial nephrectomy	[67]	0.014 (21/1455)	
Robotic partial nephrectomy	[67]	0.056 (81/1455)	
Open radical nephrectomy	[67]	0.104 (151/1455)	
Laparoscopic radical nephrectomy	[67]	0.715 (1040/1455)	
Robotic radical nephrectomy	[67]	0.037 (54/1455)	
Stage II RCC			
Open partial nephrectomy	[67]	0.019 (27/1419)	

Laparoscopic partial nephrectomy	[67]	0.003 (4/1419)	Dirichlet (27, 4, 16, 580, 766, 26)
Robotic partial nephrectomy	[67]	0.011 (16/1419)	
Open radical nephrectomy	[67]	0.409 (580/1419)	
Laparoscopic radical nephrectomy	[67]	0.540 (766/1419)	
Robotic radical nephrectomy	[67]	0.018 (26/1419)	
Stage III RCC			
Open radical nephrectomy	Expert Opinion	0.51	Uniform (0.35, 0.65)
Laparoscopic or robotic radical nephrectomy		0.49	Uniform (0.65, 0.35)
Stage IV RCC			
Cytoreductive nephrectomy	[68-74]	0.37 (18,831/50,895)	Beta (18831, 32064)
Metastasectomy	[57, 75]	0.17 (107/623)~~	Beta (107, 516)
Palliative radiotherapy for bone pain	[76, 77]	0.12 (137/1108)	Beta (137,971)
Proportion of patients receiving no systemic therapy	[63, 78-83]	0.28 (104/365)	Beta (104, 261)
Proportion receiving first line therapy	[83]	0.72 (261/365)	Beta (261, 104)
Proportion of individuals on first line therapy who receive sunitinib	[84]	0.43 (527/1229)	Beta (527, 702)
Proportion of individuals on first line therapy who receive second line therapy	[83]	0.47 (123/261)	Beta (123, 138)
Proportion of individuals on second line therapy who receive third line therapy	[83]	0.33 (41/123)	Beta (41, 82)
Unit costs			
Parameter	Source	Mean (SE) or (IQR)	Distribution
Screening costs			
Invitation (clerical staff time, postage and stationery, cost of obtaining patient details, office space and equipment)	[21]	£1.94 [€2] (0.49)	Gamma (16, 0.12)
Technician performed ultrasound	[21]	£37.53 [€47] (9.38)	Gamma (16, 2.35)
CT Abdomen & Pelvis with contrast	[26]	£115 [145€] (£88-£134)	Gamma (10.59, 10.66)
Assessment			
Clinical biochemistry	[26]	£1 [1€] (£1-£1)	Constant
Haematology	[26]	£3 [€4] (£2-£4)	Gamma (4.08, 0.77)
Phlebotomy	[26]	£3 [€4] (£2-£4)	Gamma (4.08, 0.77)
Histopathology	[26]	£31 [€39] (£15-£36)	Gamma (2.66, 10.25)
CT chest with contrast	[26]	£102 [€129] (£71-£135)	Gamma (4.70, 22.77)
CT of three areas with contrast	[26]	£121 [€153] (£88-£139)	Gamma (9.01, 12.86)
CT brain	[26]	102 [€129] (£71-£135)	Gamma (4.70, 22.77)
Outpatient renal biopsy	[26]	£158 [€199] (£125-£194)	Gamma (9.72, 16.72)
Urology outpatient clinic	[26]	£ 105.19 [€133] (10.52)	Gamma (100, 1.05)
Oncology clinic	[26]	£151 [€191] (£125-£194)	Gamma (9.72, 16.72)
MDT discussion	[26]	£107 [€135] (£71-£131)	Gamma (5.15, 20.33)

Management			
Percutaneous Cryoablation	[26]	£5,372 [€6,783] (£3,444-£6,563)	Gamma (4.67, 1113.35)
Percutaneous, Microwave or Radiofrequency Ablation	[26]	£2,952 [€3,727] (£1,706-£3,559)	Gamma (3.66, 756.08)
Laparoscopic nephrectomy (partial or radical) Cost of surgery and health care costs over one year	[85]	£6,581 [€8,309] (£6,001- £7123)	Gamma (62.33, 105.59)
Open nephrectomy (partial or radical) Cost of surgery and health care costs over one year	[85]	£8,021 [€10,127] (£7,000-£8,946)	Gamma (30.55, 262.55)
Robotic nephrectomy (partial or radical) Cost of surgery and health care costs over one year	[85]	£6,534 [€8,250] (£5,972-£7,059)	Gamma (65.32, 100.03)
Cytoreductive nephrectomy Cost of surgery and health care costs over one year	[26] Adapted from [85]	£9,938 [€12,548] (993.8)	Gamma (100, 99.38)
Metastasectomy for thoracic metastases	[26]	£6,514 [€8,225] (£4,973-£7,655)	Gamma (10.08, 637.65)
Metastasectomy for abdominal metastases	[26]	£4,101 [€5,178] (£2,538-£5,345)	Gamma (3.57, 1160.30)
Radiotherapy (preparation and delivery)	[26]	£388 [€490] (£279-£483)	Gamma (6.34, 61.79)
Annual drug costs			
Sunitinib	[81, 86]	£16,120 [€20,353]	Constant
Pazopanib	[81, 86]	£16,304 [€20,585]	Constant
Everolimus	[86, 87]	£25,765 [€32,531]	Constant
Axitinib	[86, 88]	£29,543 [€37,301]	Constant
Cabozantinib	[86, 89]	£54,002 [€68,183]	Constant
Nivolumab	[86, 90]	£57,625 [€72,757]	Constant
Lenvatinib & Everolimus	[86, 91]	£51,668 [€65,236]	Constant
Contact with the health services due to adverse events (annual cost for pazopanib)	[81]	£1,622 (162.2) [€2,048]	Beta (100, 16.22)
Contact with the health services due to adverse events (annual cost for all other therapies)	[81]	£2,144 (214.4) [€2,707]	Beta (100, 21.44)
Summary costs for health states			
Incidental hydronephrosis or renal stone		£220 [€278]	
Incidental congenital renal anomaly		£105 [€133]	
Newly diagnosed Stage I T1a		£7,510 [€9,482]	
Newly diagnosed Stage I T1b		£6,821 [€8,612]	

Newly diagnosed Stage II		£8,110 [€10,240]
Newly diagnosed Stage III		£8,595 [€10,852]
Metastasis free Stage I-III		£0
Undiagnosed RCC		£0
False positive (<4cm)		£6,889 [€8,698]
False positive (4-7cm)		£7,259 [€9,165]
False positive (>7cm)		£7,622 [€9,624]
Newly diagnosed stage IV		£4,555 [€5,751]
Newly diagnosed metastatic recurrence		£759 [€958]
No progression on 1st line ST		£19,244 [€24,297]
No progression on 2nd line ST		£47,041 [€59,394]
No progression on 3rd line ST		£47,041 [€59,394]
Stage IV, no systemic therapy	[77, 81]	£1,428 [€1,803]
Progressive disease	[77, 81]	£1,690 [€2,134]
Terminal care costs	[92]	£11,616 [€14,666]

Utilities

Parameter	Source	Mean	Distribution
Screening Ultrasound	Assumption	1 Varied in sensitivity analysis	Constant
No cancer	Assumption	1	Constant
Undiagnosed Cancer	Assumption	1	Constant
Newly diagnosed Stage I T1a	Clinical expert opinion based on [22, 93]	0.934[$$]	Beta (5.64, 0.40)
Newly diagnosed I T1b		0.934[$$]	Beta (5.64, 0.40)
Newly diagnosed Stage II		0.869[##]	Beta (12.28, 1.86)
Newly diagnosed Stage III		0.869[##]	Beta (12.28, 1.86)
Metastasis free Stages I-III		1	Constant
False positive Stage I T1a	Assumption	0.934[$$]	Beta (5.64, 0.40)
False positive Stage I T1b		0.934[$$]	Beta (5.64, 0.40)
False positive Stage II		0.869[##]	Beta (12.28, 1.86)
Stage IV, NP on 1st line therapy	[94-98]	0.78	Beta (1337.7, 377.3)
Stage IV, NP on 2nd line therapy	[77]	0.70	Beta (29.3, 12.56)
Stage IV, NP on 3rd line therapy	Assumption based on [77]	0.70	Beta (29.3, 12.56)
Stage IV, NST	[77]	0.69	Beta (500.31, 222.68)
Progressive Disease	[77]	0.61	Beta (441.03, 281.97)
Terminal, RCC Death and Non-RCC Death	Assumption	0	Constant

~Small or atrophic kidneys, aplasia, dysplasia, duplication or horseshoe kidney

*Proportions of those stage I-II

[#]Proportions of those stage I

**Relative survival, therefore this was converted to absolute survival using the age dependent probability of background mortality (see Supplement for details).

[$]Overall survival data was utilised to calculate the transition probability from each health state to death. This value was subsequently adjusted based on known age dependent background mortality to derive the transition probability for RCC death

~~It was assumed 28.8% (17/59) of individuals undergo surgical management for thoracic metastases and 71.2% (42/59) for abdominal metastases [75].

[$$]Equivalent to a utility of 0.737 for 3 months and a utility of 1 for 9 months

[##]Equivalent to a utility of 0.737 for 6 months and a utility of 1 for 6 months

476 **Table 2: Baseline results**

477 *The incremental costs (cost of screening and treatment), quality adjusted life years (QALYs)*

478 *and incremental cost-effectiveness ratio (ICER) per person screened is shown for each age*

479 *and sex.*

	Males			Females		
	40 years	50 years	60 years	40 years	50 years	60 years
Prevalence of RCC	0.14% (0.08-0.23%)	0.23% (0.12-0.37%)	0.34% (0.18-0.54%)	0.07% (0.04-0.11%)	0.09% (0.05-0.14%)	0.16% (0.08-0.25%)
Incremental costs	£47.06	£45.69	£44.55	£47.61	£46.99	£46.56
Incremental QALYs	0.00155	0.00205	0.00246	0.000809	0.000937	0.00125
ICER	£30,367	£22,277	£18,092	£58,819	£50,160	£37,327

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Table 3: Results of the two-way sensitivity analysis of age, sex, prevalence of RCC and cost of screening ultrasound

The incremental cost-effectiveness ratio (ICER) is shown for each age and sex. Values are highlighted in green if the ICER < £20,000/QALY, amber if the ICER £20,000-£30,000/QALY and red if the ICER > £30,000/QALY.

	Males			Females		
Prevalence	40 years	50 years	60 years	40 years	50 years	60 years
0.0005	£79,384	£99,763	£134,251	£77,526	£93,379	£123,795
0.001	£41,969	£49,599	£69,003	£38,733	£44,318	£57,667
0.0015	£30,359	£31,496	£46,545	£25,266	£28,901	£37,799
0.002	£20,832	£25,143	£33,320	£18,935	£22,306	£29,603
0.0025	£14,949	£18,784	£26,377	£14,592	£18,170	£22,058
0.003	£12,969	£15,546	£21,163	£12,212	£14,615	£19,429
0.0035	£9,961	£12,046	£16,676	£10,474	£12,308	£15,710
0.004	£9,154	£11,830	£15,644	£8,920	£10,399	£13,846
0.0045	£7,803	£9,990	£14,633	£7,533	£8,897	£11,548
0.005	£6,862	£8,433	£12,774	£6,611	£7,957	£10,285
0.0055	£6,209	£8,232	£11,438	£6,152	£7,413	£9,151
0.006	£5,651	£7,786	£10,123	£5,716	£6,863	£8,862
Cost of US						
£70	£47,863	£34,319	£34,000	£91,772	£85,491	£69,092
£60	£40,587	£31,717	£29,317	£81,603	£76,915	£59,227
£50	£35,309	£26,187	£24,134	£68,069	£62,299	£45,981
£40	£29,199	£21,161	£18,443	£57,431	£52,414	£38,759
£30	£23,165	£18,479	£16,061	£45,740	£42,234	£28,754
£20	£16,371	£13,141	£11,340	£37,756	£34,387	£23,083

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