National Institute for Health and Care Excellence

Kidney cancer: diagnosis and management

[F] Evidence review for follow-up of previously treated renal cell carcinoma

NICE guideline NG256

Evidence underpinning recommendations 1.11.1 to 1.11.19 and a research recommendation in the NICE guideline

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1.1 Review question

For adults who have had treatment for localised or locally advanced renal cell carcinoma, what are the most clinically and cost-effective risk-stratified* follow-up strategies (based on method, duration, and frequency)?

* Risk refers to risk of recurrence or death

1.1.1 Introduction

People who have been successfully treated for localised or locally advanced renal cell carcinoma (RCC) are deemed to be cured. They are therefore moved out of active treatment and receive follow-up, which consists of varying frequencies of imaging, and other assessments as needed, conducted over time based on their risk of recurrence. It has been reported that 20 to 30% of people undergoing surgery for non-metastatic RCC will experience either a local or distant recurrence at 5 years (Speed et al. 2017). Early detection of cancer recurrence may mean more effective treatment and improved survival. Therefore, it is important to have follow-up schedules that identify recurrence in people who have undergone treatment for RCC whilst also avoiding unnecessary burden on people of having follow-up scans too frequently. Current guidance for follow-up strategies for people who have been treated for localised or locally advanced RCC is varied and based on consensus.

This review aims to evaluate and compare the clinical and cost-effectiveness of different follow-up strategies for monitoring any long-term consequences of treatment and early detection of disease progression in adults who have been treated for localised or locally advanced RCC. In practice, follow-up is based on risk so only risk stratified (based on risk of recurrence or death) follow-up strategies will be assessed in this review.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	Inclusion: • Adults (18 years or over) who have been treated for localised or locally advanced renal cell carcinoma (RCC) Exclusion: • Adults with metastatic disease
Interventions	Risk-stratified* follow-up protocols which might include: • frequency of follow-up • method of follow-up (e.g., type of imaging) • duration of follow-up * Risk refers to risk of recurrence or death. A tiered approach will be taken for this work:

	• Follow-up strategies using risk stratified models that have been judged to be clinically useful (have good discrimination) by the committee in the review on prognosis risk tools will be included. • If studies using these models are not available, then any risk stratified follow-up strategy will be included.
Comparator	Different risk stratified follow-up protocols compared to each other.

Outcomes	• Survival:
	  ○ Disease-free survival, including cancer-free survival
	  ○ Overall survival, or if not reported, mortality
	  ○ Cancer specific survival, or if not reported, cancer specific mortality
	• Local recurrence
	• Distant recurrence
	• People with recurrence who require systemic treatment
	• People with recurrence who are suitable for curative treatment
	• People with recurrence who go on to have surveillance
	• Quality of life
	• Long term consequences of treatment, for example:
	  ○ renal function impairment reported as glomerular filtration rate
	  ○ cardiovascular events

Study type	Systematic reviews of randomised controlled trials (RCTs) and RCTs. If RCTs are not available, then systematic reviews of non-randomised comparative studies and primary non-randomised comparative studies will be included. These are expected to include respective cohort studies based on registry data.

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods and technical decisions specific to this review question are described in the review protocol in appendix A and the methods chapter.

Methods and technical decisions specific to this review are summarised below:

1. Due to the lack of extractable data available for the outcomes of interest narrative outcomes were accepted for survival outcomes.

2. Subgroup analysis could not be conducted because none of the included studies provided data on subgroups of interest.

3. For outcomes where the line of no effect was defined as the minimal important difference (MID), we planned to use a relevant RCT to determine the minimum sample size needed for consideration for the second downgrade criteria for the imprecision domain in GRADE. No relevant RCTs reporting power calculations were identified so the committee agreed to use the same minimum sample size of 420 that was used for review A (the review covered the clinical and cost effectiveness of partial compared with radical nephrectomy in adults with localised RCC).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 07/10/2024 and re-run on 17/04/2025. The following databases were searched: Cochrane CENTRAL (Wiley), Cochrane CDSR (Wiley), Embase (Ovid), Epistemonikos (Epistemonikos), Medline ALL (Ovid). Full search strategies for each database are provided in appendix B. Limits were applied to remove animal papers, non-English language papers and conference abstracts. Filters were used to limit to OECD countries, systematic reviews, randomised controlled trials and observational studies

The searches for the cost effectiveness evidence were run on 14/10/2024 and re-run on 07/05/2025. The following databases were searched: Econlit (Ovid), Embase (Ovid), NHS EED (CRD York), International Health Technology Assessment Database (INAHTA), Medline ALL (Ovid). Filters were used to limit to OECD countries, cost utility, health state utility and cost effectiveness studies.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement. Further details and full search strategies for each database are provided in appendix B.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 3, 297 references (see appendix B for the literature search strategy).

These 3,297 references were screened at title and abstract level against the review protocol, with 3,260 excluded at this level as they did not meet the criteria for inclusion detailed in the review protocol. 10% of references were screened separately by two reviewers with 99% agreement. Discrepancies were resolved by discussion.

The full texts of 26 cohort studies, 5 review articles, 3 systematic reviews and 2 editorial comments and 1 protocol were ordered for closer inspection. Two cohort studies (Dabestani et al. 2019 and Gires et al. 2019) met the criteria specified in the review protocol (appendix A). One was reported across two papers (Dabestani et al. 2019a, 2019b). For a summary of the 2 included studies see Table 2.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of studies included in the effectiveness evidence

Study details	Population/setting	Intervention	Comparator	Outcomes	Risk of bias	Other comments
Dabestani (2019a) Follow-up time (median [interquartile range]): 63 (58–76) months Retrospective cohort	N=1,612 consecutive people with non-metastatic RCC treated with curative intent at 12 institutes across eight European countries between 2006 and 2011	• Cross sectional imaging (CT or MRI) as a percentage of total number of imaging tests ≥ 50% (conventional imaging included chest x-ray or ultrasound). • Above median imaging frequency	• Cross sectional imaging (CT or MRI) as a percentage of total number of imaging tests < 50% (conventional imaging included chest x-ray or ultrasound) • Below median imaging frequency	Recurrence (detection of non-symptomatic recurrence or detection within institutional follow-up out of the total number of recurrences) Overall survival (narrative results only)	Serious	People were stratified into low-, intermediate-, and high-risk groups according to the Leibovich score in cases of predominantly clear cell RCC, and the UISS system for non–clear cell RCC subtypes. Study also reported the median (interquartile range) number of imaging studies by risk group (low/intermediate/high), follow-up duration (short/mid/long-term) and recurrence/non-recurrence. This data did not fit the protocol as it was not a relevant comparison and results were not analysable. Limitations: Indirectness of intervention - the follow-up received was not based on pre-specified protocol according to risk. Each of the institutions had their own follow-up protocols with varying

Study details	Population/setting	Intervention	Comparator	Outcomes	Risk of bias	Other comments
						intervals between each imaging. Imaging methods varied.
Dabestani (2019b) Follow-up time (median [interquartile range]): 63 (58–76) months Retrospective cohort	N=1,612 consecutive people with non-metastatic RCC treated with curative intent at 12 institutes across eight European countries between 2006 and 2011	Cross sectional imaging (CT and MRI) and conventional imaging (chest x ray and ultrasound) – imaging without following specific guideline for follow-up	Imaging according to the 2017 EAU guidelines for follow-up recommendations. Image ratio (number of imaging scans people received divided by the recommended number of images they should have undergone until recurrence or last follow-up based on EAU guidelines): ≤0.75 vs.0.76-1.99 vs. ≥2.0	Overall survival (narrative results only)	Serious	People were stratified into low-, intermediate-, and high-risk groups according to the Leibovich score in cases of predominantly clear cell RCC, and the UISS. system for non–clear cell RCC subtypes. Study also reported the number of imaging procedures needed for detection of one person undergoing treatment with curative intent for recurrent RCC and for one person alive with no evidence of disease after treatment of their recurrence. This data did not fit the protocol as it was not a relevant comparison and results were not analysable. Limitations: There was lack of information and no specific follow-up protocol for the cross-sectional imaging intervention group.
Gires (2019)	N=267 people who underwent radical or partial nephrectomy for renal tumour from	“Adequate" follow-up defined as anything corresponding	"Inadequate" follow-up defined as imaging examinations	Recurrence free survival (narrative results only)	Moderate	The UISS was used to stratify people into low-, intermediate- and high- risk groups.

Study details	Population/setting	Intervention	Comparator	Outcomes	Risk of bias	Other comments
Follow-up time (median [interquartile range]): 72 (51-92) months Retrospective cohort	2006 to 2010 in an academic department of urology, France	precisely to the recommendations of the UISS surveillance protocol	more spaced out/delayed/less informative than what is recommended in the UISS surveillance protocol	Cancer-specific survival after recurrence (narrative results only) Overall survival (narrative results only)		Factors considered in multivariable analysis: - age at recurrence - gender - symptoms at recurrence - stage - pN + status - histological subtype (clear cells/papillary/chromophobe) - type of recurrence (single/oligo/multi) Limitations: indirectness of comparator; vagueness in reporting of what “inadequate” follow-up entailed.

EAU, European Association of Urology; RCC, renal cell carcinoma; UISS, University of California Los Angeles Integrated Staging System

UISS protocol is a risk-based follow-up protocol for people treated with surgical resection of localised or locally advanced renal tumour. The protocol follows people up for up to 108 months and involves the use of CT scans of the chest and abdomen.

See appendix D.

1.1.6 Summary of the effectiveness evidence

Interpreting the effectiveness evidence

In the absence of published minimally important differences (MIDs) clinical decision thresholds were agreed with the committee and used to

interpret the evidence. The line of no effect (in this case represented by 1.0) was used as a clinical decision threshold for the outcomes of recurrence, cancer-specific survival. No data was identified for people with recurrence who require systemic treatment, people with recurrence suitable for curative treatment, people with recurrence who go on to have surveillance, long-term consequences of treatment including renal function impairment and cardiovascular events, quality of life using the EORTC Core Quality of Life Questionnaire (QLQ-C30), EQ-5D or VAS scores (the only outcomes with a published MID).

The following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables:

For outcomes without a published MID or where the clinical decision thresholds are set as the line of no effect evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- It is not possible from the evidence to differentiate between comparators if the 95% CI crosses the line of no effect.

Narrative data was also identified for cancer specific survival, overall survival and recurrence free survival and is presented below. It was not possible to assess the certainty of this data using GRADE however the risk of bias was assessed for these studies.

See appendix F for full GRADE tables.

Table 3: Summary GRADE table for 50% or more cross-sectional imaging versus less than 50% cross-sectional imaging – overall risk group

Number of studies	Outcome	Sample size	Effect estimate	Certainty	Interpretation of effect
1 (Dabestani 2019a)	Non-symptomatic recurrences (out of total recurrences)	336	RR 1.09 (0.82 to 1.45)	Very low	Could not differentiate
1 (Dabestani 2019a)	Recurrences detected in regular follow-up (out of total recurrences)	336	RR 1.26 (1.08 to 1.48)	Very low	Effect favours ≥50% cross-sectional imaging

Reasons for downgrading can be found in full GRADE tables in appendix F.

Table 4: Summary GRADE table for high (above median) imaging frequency versus low (below median) imaging frequency – overall risk group

Number of studies	Outcome	Sample size	Effect estimate	Certainty	Interpretation of effect
1 (Dabestani 2019a)	Non-symptomatic recurrences (out of total recurrences)	316	RR 1.18 (1.00 to 1.39)	Very low	Could not differentiate
1 (Dabestani 2019a)	Recurrences detected in regular follow-up (out of total recurrences)	280	RR 1.23 (1.05 to 1.45)	Very low	Effect favours high frequency imaging

Reasons for downgrading can be found in full GRADE tables in appendix F.

Table 5: Summary GRADE table for "inadequate" follow-up (imaging <UISS recommendations) versus “adequate" follow-up (UISS surveillance protocol)

Number of studies	Outcome	Sample size	Effect estimate	Certainty	Interpretation of effect
1 (Gires 2019)	Cancer-specific survival after recurrence	62	HR 1.13 (0.53 to 2.41)	Very Low	Could not differentiate

Reasons for downgrading can be found in full GRADE tables in appendix F.

Narrative results

- One study with serious risk of bias (Dabestani et al. 2019a) reported no statistically significant difference in overall survival between potentially curable and probably incurable* people stratified for the type of imaging resulting in detection of their recurrence. The same study reported no statistically significant difference in overall survival after recurrence based on high (≥50%) or low (<50%) cross-sectional imaging percentage during follow-up.

* Potentially curable was taken to be local recurrence, single metastasis or oligometastatic (≤ 3 lesions at a single site). All other recurrence was considered probably incurable.

- One study with serious risk of bias (Dabestani et al. 2019b, N=1,612) reported no significant differences in overall survival after recurrence for people with imaging ratio* of ≤0.75, 0.76-1.99 and ≥2.0.

  *Defined as the total number of imaging scans divided by recommended number of imaging scans (from the EAU 2017 guideline).

- One study with moderate risk of bias (Gires et al. 2019) reported no significant differences between those receiving “adequate” and “inadequate” follow-up in recurrence free survival (log rank, p=0.93), cancer-specific survival (log rank, p=0.46), or overall survival (log rank, p=0.91).

1.1.7 Economic evidence

A literature review was conducted to identify published economic evaluations on risk-stratified follow-up regimens (see appendix B).

This search retrieved 133 studies. Based on title and abstract screening for this review question, one study was considered for full text screening but was excluded at full text review.

Due to the perceived economic importance of this review question, an original economic analysis was conducted (1.1.9 Economic model).

1.1.7.2 Excluded studies

One study (see appendix J) was considered at full text screening but was excluded, primarily because the study did not compare costs between different follow-up regimens and was from a US cost perspective.

1.1.8 Summary of included economic evidence

No relevant economic evidence was identified.

1.1.9 Economic model

An original cost-utility model was developed to assess the cost-effectiveness of different follow-up strategies for people who have been treated for localised or locally advanced RCC. This economic analysis was conducted from the perspective of UK NHS and personal social services (PSS).

The committee agreed that this review question should be prioritised for original economic modelling due to the likely high resource impact given the large population size considered by this review, and the potential associated costs of monitoring people over several years. Many existing guidelines for follow-up are stratified by risk group, as people with higher rates of recurrence are expected to benefit from more frequent monitoring. The results from the RECUR database analysis (Dabestani et al. 2019) suggested that increased imaging scans during follow-up were not generally associated with improved survival benefits after recurrence for the overall population. However, the RECUR data was not analysed in this way for risk subgroups, but other risk-stratified analyses of the dataset suggested that certain strategies may be more efficient at detecting non-symptomatic recurrences than symptomatic recurrences.

This model was a cost-utility analysis conducted over a 25-year lifetime horizon, comparing outcomes of different follow-up strategies:

- One analysis compared outcomes of a high proportion of cross-sectional imaging strategy versus a low proportion of cross-sectional imaging strategy (“high CSI” and “low CSI”).
- The second analysis compared outcomes of a low imaging frequency strategy versus a high imaging frequency strategy (“low IF” and “high IF”).

The population considered in the analysis was people who have previously undergone nephrectomy for treatment of localised or locally advanced RCC and had successful removal of their tumour. The population was further analysed by whether they were at low, intermediate or high risk of recurrence or progression, based on their initial tumour characteristics using validated risk tools.

Clinical outcomes in the model were modelled using data from on the clinical evidence from an analysis of the RECUR database. The RECUR database includes retrospectively collected data from people with non-metastatic RCC who underwent surgery with curative intent. Data was collected in eight European countries, including the UK, during the period from January 2006 to December 2011 with a median follow-up period of 61.9 (IQR: 51.9-74.2) months (Dabestani et al. 2019). 76.1% of people in RECUR had clear cell RCC, 14% had papillary RCC and 7.0% had chromophobe RCC. Risk stratification of people in this retrospective study was based on Leibovich 2003 or the UICC scoring system for clear cell and non-clear cell RCC, respectively. Recurrences were categorised into potentially curable recurrence (defined as isolated local, solitary distant metastatic, or oligometastatic (three or fewer lesions at a single site) and probably incurable recurrence.

Main cost-effectiveness outputs were costs, health outcomes (in quality-adjusted life-years; QALYs), and incremental cost-effectiveness ratios (ICERs).

The economic model evidence summary is shown in Table 6.

Table 6: Guideline economic model evidence summary table

Study design and type of analysis	Population	Interventions and comparators	Perspective	Primary outcome	Time horizon	Applicability and limitations
Study design: Decision analytic model (a de-novo semi-Markov model) Type of analysis: cost-utility analysis	Adults with localised or locally advanced RCC who had previously undergone nephrectomy and had successful tumour removal.	• a high proportion of cross-sectional imaging strategy versus a low proportion of cross-sectional imaging strategy • a low imaging frequency strategy versus a high imaging frequency strategy	NHS/PSS	Total discounted costs and QALYs, ICER	Lifetime	Directly applicable Minor limitations[1]

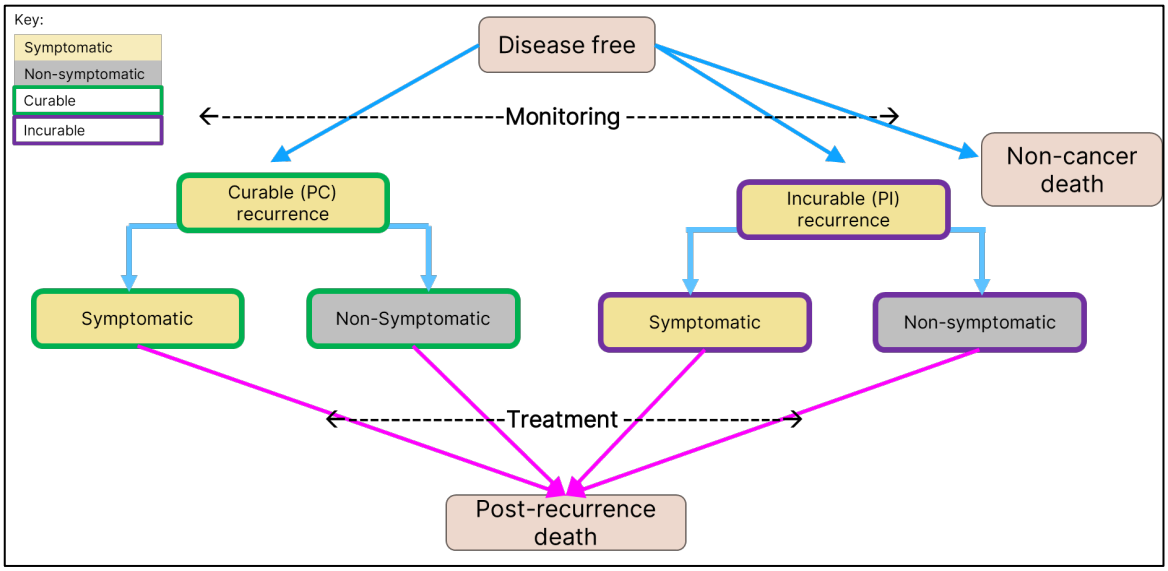
Abbreviations: RCC: renal cell carcinoma; PSS: personal social services; QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio

1. low quality and uncertainty around clinical effectiveness evidence used to inform the economic model

Model structure

All people start from the disease-free health state following a radical or partial nephrectomy (Figure 1). They face a risk of curable recurrence or incurable recurrence according to their risk group. For each type of recurrence, people may present as being symptomatic or non-symptomatic, which is conditional on the follow-up strategy and risk group. Lesions detected earlier are more likely to be non-symptomatic and have a better prognosis than symptomatic ones. The probability of a detected recurrence being symptomatic was associated with the follow-up strategy but assumed to be constant over time and constant between curable and non-curable recurrence. People may either experience non-cancer death from the disease-free health state, or post-recurrence death which was conditional on the symptom and curable status of the lesion.

Figure 1 Economic model diagram



Data sources

Time-varying and risk-based cumulative rates of curable and incurable recurrence were estimated using data from the RECUR database. The 10-year rate of recurrence was 8%, 22% and 53% in the low, intermediate and high-risk groups, respectively. Time-varying rates of overall survival after recurrence were taken from the RECUR database to capture the differences between symptomatic and non-symptomatic detection associated with curable and incurable recurrences. Parametric models were fitted to the Kaplan-Meier (KM) plots for the recurrence and survival outcomes to estimate survival during the observed period and to extrapolate survival beyond observed period over the patient's lifetime. Selection of survival model was based on statistical fit and clinical plausibility of survival predictions.

The probability of a recurrence being symptomatic or non-symptomatic for each monitoring strategy was derived from the clinical review, which was based on the RECUR database (Figure 5 and Figure 7). In the low- and intermediate-risk groups, the high CSI and the high IF strategies had a greater probability of detecting a recurrence that was non-symptomatic, compared with the low CSI and the low IF strategies. The probability that a recurrence detected by a high-CSI strategy is non-symptomatic was lower than the low-CSI strategy,

which is counter to expectations given the greater accuracy of CSI. The quality and certainty of the clinical evidence was assessed to be very low, and there were no statistically significant differences between follow-up strategies. The point estimate of the probability of detecting a non-symptomatic recurrence was used in the economic model base case analysis to provide an estimate of the base case ICER. In the probabilistic analysis, the probability of detecting a non-symptomatic recurrence was sampled from the distribution estimated in the forest plot, to estimate the probability that a follow-up strategy is cost-effective.

Quality of life associated with each model health state was estimated based on the treatment that people received in each health state. Utility data was taken from other published RCC models, including the NICE technology appraisal of adjuvant pembrolizumab (TA830) and the NICE RCC pathway pilot (TA964).

Costs of monitoring and recurrence management were estimated using unit costs and resource use associated with each health state. Unit costs were estimated from published national sources, such as the BNF for drug costs, NHS Cost Collection for hospital episode, outpatient and imaging costs, and PSSRU for staffing costs.

The number of scans for each follow-up strategy being compared was estimated using data from the RECUR database. Total scan costs for each follow-up strategy in each risk category were calculated as a weighted average of the different types of imaging and their respective unit costs. All RECUR institutes used their own follow-up protocols with varying intervals between each imaging. The high IF group was defined by people who received higher than the median number of scans in RECUR, and the low IF group was defined by people who received lower than the median. The median number of scans per year in RECUR was 2.08 in the low-risk group, 2.41 in the intermediate-risk group, and 3.32 in the high-risk group (median total scans not reported). The low CSI group was defined as less than 50% of scans being CT or MRI.

Management of recurrence was informed by RECUR data. People could receive palliative treatment (either systemic anti-cancer therapy [SACT] or best supportive care [BSC]) or observation. For people with incurable recurrence, they could also receive metastasectomy, followed by observation. People with curable recurrence could receive metastasectomy, SABR or ablation, followed by observation.

Results of the cost effectiveness analysis

Results of the base-case cost effectiveness analysis are presented in Table 7.

In all three risk groups, the high CSI strategy had higher mean lifetime costs compared with the low CSI strategy, due to higher costs of CT and MRI relative to ultrasound and X-ray. In the low-risk and intermediate-risk groups, the low CSI strategies were also associated with lower mean lifetime QALYs, as they had a lower probability of detecting non-symptomatic recurrences, which are associated with greater survival than symptomatic recurrences. The high CSI strategy had a cost per QALY of £3,231 in the low-risk group and of £4,919 in the intermediate-risk group, suggesting that it is an efficient use of NHS resources in these risk groups.

In the high-risk group, the low CSI strategy was associated with higher mean lifetime QALYs, as it had a higher probability of detecting non-symptomatic recurrences than the high CSI strategy (conversely to the probability in the low-risk and intermediate-risk groups). The

analysis suggests that the low CSI strategy was the dominant strategy in this risk group, and that it is the more efficient use of NHS resources.

In all three risk groups, the low IF strategies had lower mean lifetime costs compared to the high IF strategies, due to a reduction in imaging costs. However, they are also associated with lower mean lifetime QALYs. The high IF strategy had a cost per QALY of £14,674 in the low-risk group, and £11,710 in the intermediate-risk group, suggesting that it is an efficient use of NHS resources in these risk groups as interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective.

In the high-risk group, the cost per QALY for the high IF strategy was estimated to be £25,684. Interventions with ICERs between £20,000 and £30,000 require greater certainty in the analysis or consideration of uncaptured benefits. While the estimates of the probability of detecting a non-symptomatic recurrence was not statistically significant in all risk groups, the point estimates favoured high IF in all groups. However, the risk ratio was greatest in the low-risk group and lowest in the high-risk group.

The probability of a strategy detecting a non-symptomatic recurrence was highly uncertain in all analyses, as they were based on small patient numbers and the quality of the evidence in relation to this review question was assessed as being very low. For the majority of estimates, these were not estimated as being statistically significant. The impact of that uncertainty is explored in a sensitivity analysis.

Table 7: Base-case cost effectiveness results

Strategy	Total cost	Total QALYs	NHB	Inc. NMB	ICER	Probability cost effective
Low-risk group						
Higher vs lower proportion cross-sectional imaging						
<50% CSI	£1,939	12.46	12.37	-	-	-
>50% CSI	£2,148	12.53	12.42	£1082	£3,231	100%
Higher vs low intensity of imaging frequency						
Low intensity	£1,635	12.47	12.39	-	-	-
High intensity	£2,401	12.52	12.40	£278	£14,674	73%
Intermediate-risk group						
Higher vs lower cross-sectional imaging						
<50% CSI	£2,547	11.23	11.10	-	-	-
>50% CSI	£2,766	11.27	11.13	£670	£4,919	99%
Higher vs low intensity of imaging						
Low intensity	£2,150	11.22	11.11	-	-	-
High intensity	£3,133	11.3	11.14	£696	£11,710	85%

High-risk group						
Higher vs lower cross-sectional imaging						
<50% CSI	£3,241	8.14	7.98	-	-	-
>50% CSI	£3,284	8.06	7.89	-£1,665	Dominated	0%
Higher vs low intensity of imaging						
Low intensity	£2,844	8.08	7.93	-	-	-
High intensity	£3,677	8.11	7.92	-£184	£25,684	47%

Key parameters were varied in a one-way sensitivity analysis to demonstrate which parameters had the greatest influence on the cost effectiveness results. Tornado diagrams in Figure 2 and Figure 3 illustrate the ten parameters that had the greatest influence on the cost effectiveness results in each analysis comparison. The impact on the results is presented as the change in incremental net monetary benefit (iNMB), where “lower iNMB” and “upper iNMB” refer to the results of the scenario using the lower and higher range of the parameter being explored, respectively.

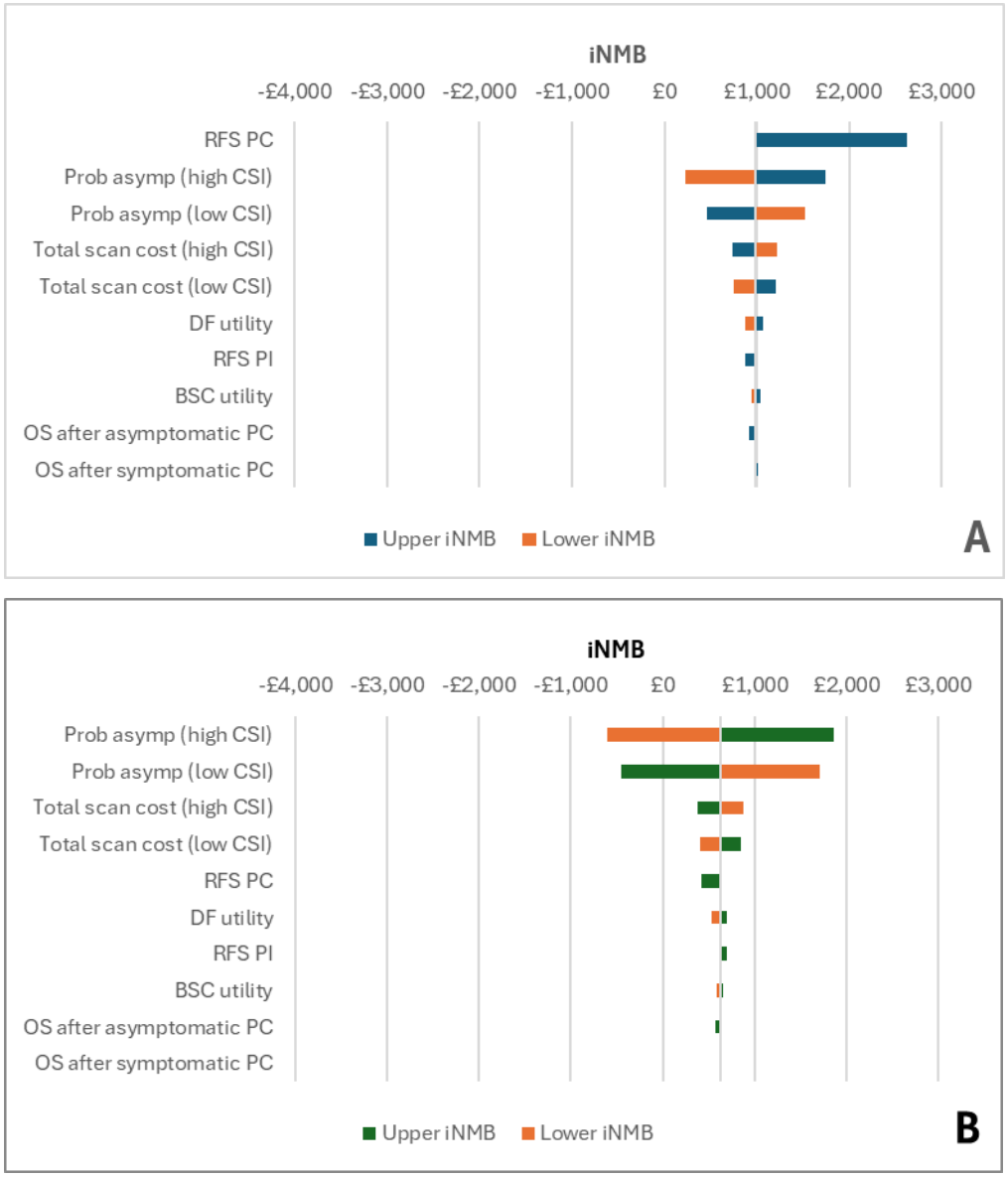
In both analyses, the parameters that had the greatest influence on the cost effectiveness results were the probability that an imaging strategy detects a non-symptomatic recurrence (compared to a symptomatic recurrence), the total cost of imaging, and the time to curable recurrence. Parameters relating to the management or evaluation of recurrences (such as overall survival following a recurrence, time until non-symptomatic recurrences developed symptoms, BSC utility value, cost of SACT had little impact on the cost effectiveness results.

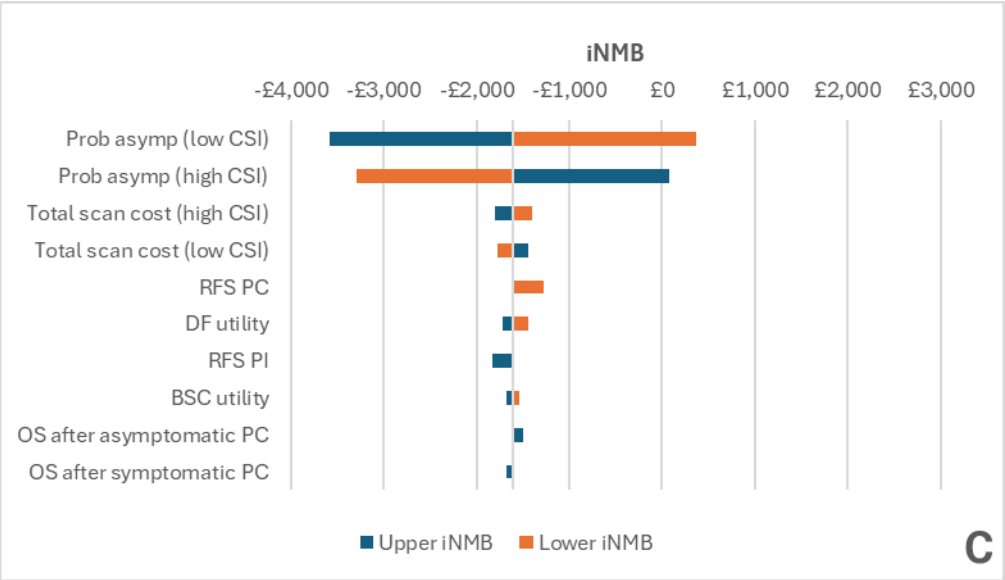
The high CSI strategy remained cost effective compared to the low CSI strategy under all scenarios in the low-risk group. In the intermediate-risk group, the low CSI strategy became cost effective compared to the high CSI strategy under two alternative assumptions: when the probability that a detected recurrence was non-symptomatic for the low CSI strategy increased by 20% from 0.62 to 0.74, or when the probability that a detected recurrence was non-symptomatic for the high CSI strategy decreased by 20% from 0.71 to 0.57 (i.e. the low CSI strategy had a greater probability of detecting a non-symptomatic recurrence than the high CSI strategy). In the high-risk group, the high CSI imaging strategy became cost effective with a higher probability of detecting non-symptomatic recurrence for the high CSI group or a lower probability for the low CSI group, compared with the base case.

Likewise, we varied key parameters such as the probability of detecting a non-symptomatic recurrence and costs of imaging for IF strategy by 20% relative to the corresponding base-case values for each risk group. The high IF strategy was cost effective in the base case analysis, but it became not cost effective when the high IF strategy had a low probability or the low IF strategy had a high probability of detecting non-symptomatic recurrence, or if the high IF strategy had higher costs of imaging.

In the intermediate-risk group, the high IF strategy was cost effective in the base case analysis, but it became not cost effective when the high IF strategy had a lower probability or the low IF strategy had a higher probability of detecting non-symptomatic recurrence. In the high-risk group, the high IF strategy was not cost effective in the base case analysis, but it became cost effective with a higher probability of detecting non-symptomatic recurrence for the high IF group or a lower probability for the low IF group.

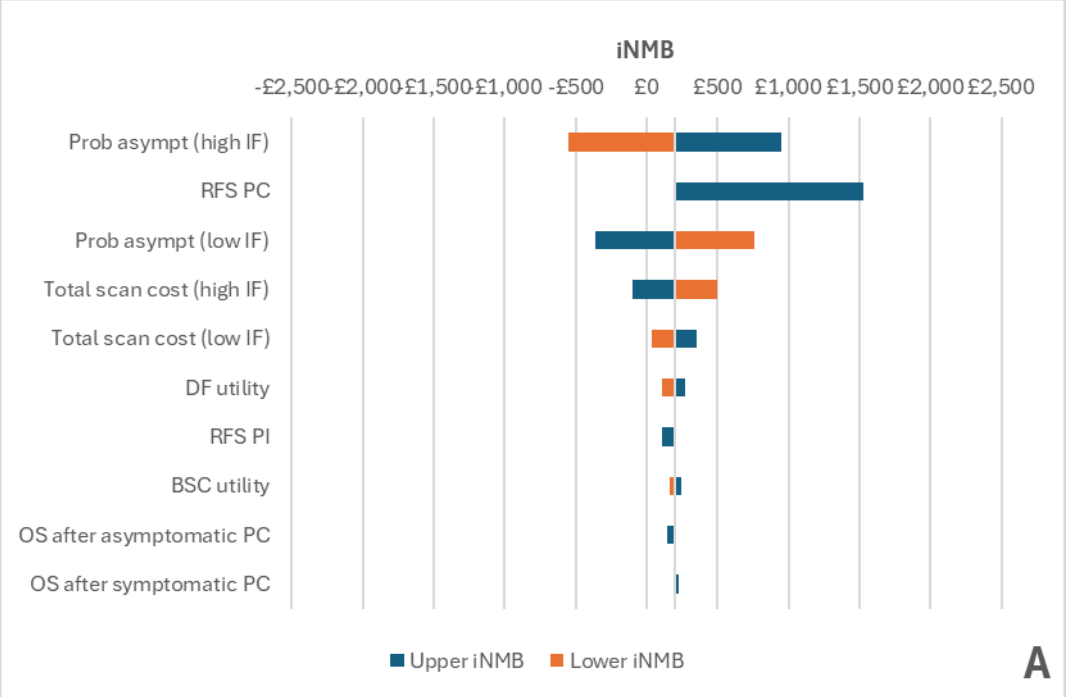
Figure 2 Sensitivity analysis: high CSI vs low CSI imaging strategy

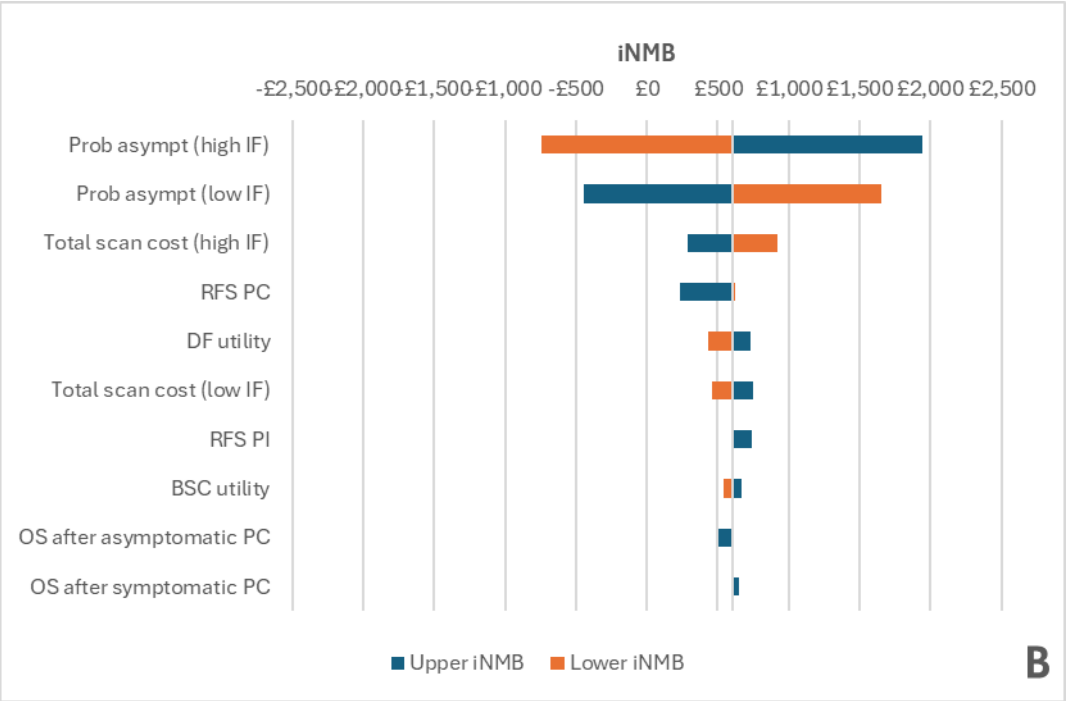


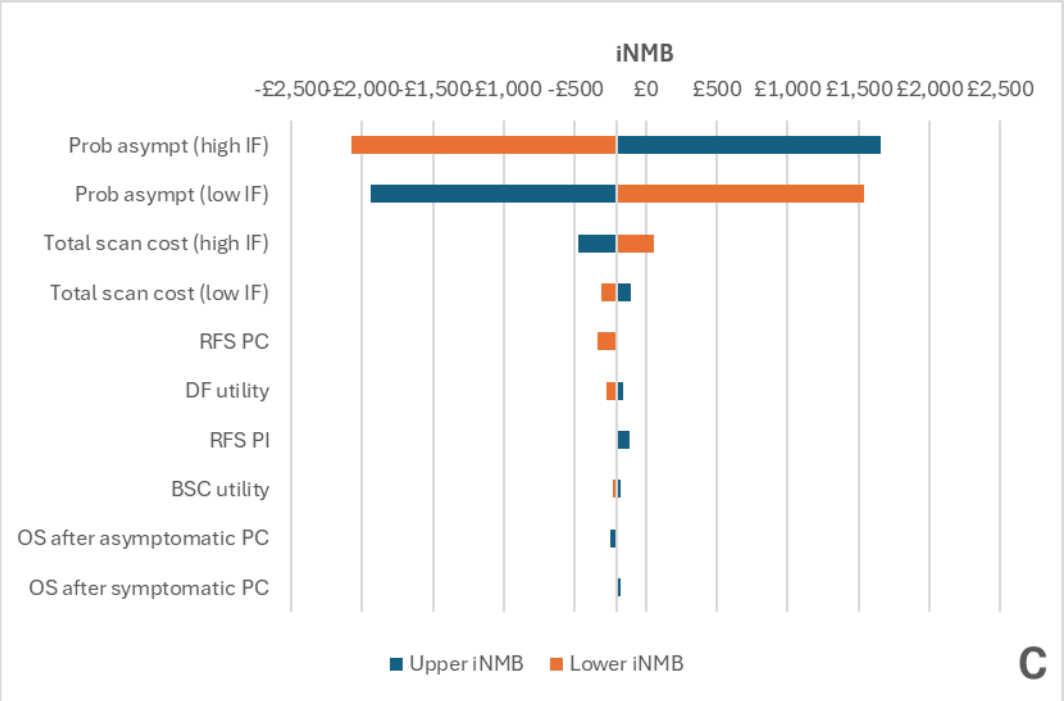


A = low-risk subgroup, B = intermediate-risk subgroup, C = high-risk subgroup.
Abbreviations: iNMB = incremental net monetary benefit, IF = imaging frequency, PC = potentially curable recurrence, DF = disease-free, RFS = recurrence free survival, PI = probably incurable recurrence, OS = overall survival. Upper iNMB refers to the iNMB when the higher value of the variable is applied; lower iNMB refers to the iNMB when the lower value of the variable is applied.

Figure 3: Sensitivity analysis: high vs low intensity imaging frequency







A = low-risk subgroup, B = intermediate-risk subgroup, C = high-risk subgroup.
Abbreviations: iNMB = incremental net monetary benefit, IF = imaging frequency, PC = potentially curable recurrence, DF = disease-free, RFS = recurrence free survival, PI = probably incurable recurrence, OS = overall survival. Upper iNMB refers to the iNMB when the higher value of the variable is applied; lower iNMB refers to the iNMB when the lower value of the variable is applied.

1.1.10 Unit costs

The costs of resources used during follow-up are presented in Table 8.

Table 8: Unit costs of imaging

Resource	Unit costs	Source
CT-CAP	£123.03	NHS Cost Collection (2024). RD26z Computerised Tomography Scan of Three areas with contrast
MRI (with contrast)	£202.40	NHS Cost Collection (2024). RD05z Magnetic Resonance Imaging Scan of Two or Three areas with contrast
MRI (without contrast)	£153.84	NHS Cost Collection (2024). RD04z Magnetic Resonance Imaging Scan of Two or Three areas without contrast
Ultrasound scan	£53.32	NHS Cost Collection (2024). RD41z Ultrasound Scan with duration of less than 20 minutes with contrast
Blood tests	£3.10	NHS Cost Collection (2024). DAPS PATH05 total haematology

CT-CAP: computed tomography scan of chest, abdomen and pelvis. MRI: magnetic resonance imaging

1.1.11 Evidence statements

- An original cost-utility analysis comparing a strategy with a high proportion of cross-sectional imaging, with a strategy with a low proportion of cross-sectional imaging found that for low-risk and intermediate-risk groups, the high CSI strategy is likely to be considered cost-effective at a threshold of £20,000 per QALY, with ICERs of £3,231 and £4,919, respectively. For the high-risk group, the high CSI strategy was associated with higher costs and lower QALYs than the low CSI strategy.
- An original cost-utility analysis comparing a strategy with a high frequency of imaging with a strategy with a low frequency of imaging found that for low-risk and intermediate-risk groups, the high-intensity strategy is likely to be considered cost-effective at a threshold of £20,000 per QALY, with ICERs of £14,674 and £11,710, respectively. For the high-risk group, the high-intensity strategy had an ICER of £25,684 compared with the low-intensity strategy, which is less likely to be considered cost-effective at a threshold of £20,000 per QALY.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee discussed the outcomes specified in the protocol and they agreed that the most important outcomes for this review were survival outcomes, particularly disease-free survival but also overall survival and cancer-specific survival. They also agreed that quality of life assessment was very important as follow-up protocols have the potential to impact people's mental well-being by inducing stress and anxiety with regular assessments but agreed that identifying a recurrence before it becomes symptomatic has the potential to improve someone's quality of life.

The committee agreed that while recurrence outcomes including local recurrence, distant recurrence, people with recurrence who require systemic or curative treatment and people with recurrence who go on to have surveillance were important, they do not necessarily correctly predict survival due to the potential impact of lead time bias which occurs when survival time appears longer due to an earlier diagnosis regardless of whether the person actually lives longer. The committee also agreed that assessing the long-term clinical consequences of treatment such as renal function impairment and cardiovascular events would be of interest as these would provide information on the downstream effect of identifying a recurrence.

1.1.12.2 The certainty of the evidence

There was limited evidence reported for the outcomes of interest outlined in the protocol. No evidence was identified for quality of life, long-term consequences of using the treatment and consequences of recurrence such as suitability for curative treatment and subsequent surveillance. The evidence for survival (overall survival and cancer specific survival) was sparse and not reported in a way that could be presented as a forest plot or combined in a meta-analysis (point estimates were not reported).

Overall, the certainty of the evidence for all outcomes was rated as very low. The evidence was downgraded due to risk of bias assessed using the ROBINS-I tool. The issues with risk of bias were often due to confounding that may have been present between the two arms examined, with more intensive follow-up arms potentially having more serious disease. Stratification of the sample by risk (conducted in Dabestani et al. 2019a, 2019b) is unlikely to have removed the effects of confounding completely. The frequencies of imaging and methods of imaging varied within the cross-sectional imaging (CSI) and conventional groups, and centres used different intervals for imaging. The follow-up times provided in the Dabestani et al. (2019a, 2019b) papers were also categorised into three groups according to ranges of follow-up, meaning it was not possible to know the exact follow-up time. Gires et al. (2019) used a Cox regression model for statistical analysis and confounding domains; however insufficient information was provided on what confounding variables it adjusted for. Dabestani et al. (2019a, 2019b) did not account for participants with incomplete follow-up in their analyses and excluded participants with <4 years follow-up data.

The evidence was downgraded for inconsistency as outcomes were contributed to by a single study. Outcomes were downgraded for imprecision when the confidence intervals crossed one or more decision making thresholds. The evidence was further downgraded for outcomes from one study (Dabestani et al. 2019a) as the follow-up protocol allocation was not based on a pre-specified protocol to which people were allocated based on risk. The different “follow-up groups” each contained a mixture of low-, medium- and high-risk individuals. Outcomes from another study, Gires et al. (2019) was downgraded for indirectness due to an indirect comparison; a risk stratified follow-up protocol was compared with any follow-up strategy that was less than what was recommended by the risk-stratified protocol.

1.1.12.3 Benefits and harms

Limited evidence

The included studies were published with a different aim to this evidence review and did not directly compare two pre-specified follow-up protocols, making the evidence provided by

them indirectly relevant to this review. This is reflected in the GRADE rating. Therefore, the committee decided to make a research recommendation for comparative studies, preferably RCTs, comparing risk of recurrence stratified follow-up strategies for people who have been treated for local or locally advanced RCC (see appendix K).

The committee acknowledged that it did not expect a large high-quality evidence base for this review and that most cancer types are lacking evidence in this area. As the evidence base was very small and had many limitations (discussed above), the committee were cautious about drawing conclusions from it to base their recommendations on. The health economic modelling (see section on 1.1.12.4 Cost effectiveness and resource use) was also based on these studies and there was a lot of uncertainty around the results of this modelling due to the associated uncertainty in the effectiveness evidence. As a result, the committee agreed that the evidence was of limited use and relied more on consensus based on their expertise when drafting recommendations.

Testing before follow-up

The committee highlighted the need for blood and urine tests after people with RCC have been treated for the primary lesion, to detect any renal insufficiency that has been caused by the treatment as that might need separate management and could affect the type of follow up imaging that is suitable for the person. The committee recommended that estimated glomerular filtration (eGFR) creatinine testing is carried out after treatment is completed but before follow-up begins. They agreed that eGFR testing should be carried out in secondary care and if it is less than 60 ml/minute/1.73m^2, the primary care should be informed to allow them to carry out an albumin–creatinine ratio (ACR). The committee cross-referred to NICE's guideline on chronic kidney disease for guidance when there is evidence of chronic kidney disease and referral criteria to specialist services.

Current practice and imaging schedules for follow-up

The included studies suggested that a higher proportion (≥ 50%) of imaging involving cross-sectional imaging (CSI) may not result in a difference in recurrence detection or overall survival when compared to a lower proportion of imaging being CSI. There was also no difference in recurrence detected with higher imaging frequency (above the median). One study (Dabestani et al. 2019b) showed that more intensive imaging frequency above what is recommended in the 2017 EAU guidance is unlikely to result in an improvement in overall survival after recurrence. The evidence from the included studies was indirect as they did not directly compare two distinct follow-up protocols, so the committee were cautious when drawing conclusions from them. The committee discussed the possible impact of lead time bias on the evidence, which may explain why the increase in imaging frequency has not resulted in improved survival outcomes for individuals. The committee noted that included studies were conducted prior to adjuvant treatment being more common in practice so although increased detection of recurrence did not translate to improved survival outcomes in the included studies, future studies where adjuvant treatments are more common in practice may show improved survival outcomes when recurrence is detected or detected earlier.

The committee discussed the commonly held belief that earlier detection of recurrence is beneficial because it means faster access to treatment and ultimately improved cancer outcomes. They noted that the limited evidence available does not seem to support this. They noted that early detection campaigns are generally aimed at primary disease where there is reasonable evidence that early detection results in an increased likelihood of receiving suitable treatments and ultimately better cancer outcomes. However, for recurrence

after treatment the evidence is sparse for cancer outcomes, and it may be that the characteristic of the lesion (for example, tumour grade) dictates the outcome rather than how early the recurrence is detected. There is therefore some uncertainty about the degree of benefit in detecting a recurrence using regular imaging during a follow-up period compared to waiting until it is picked up another way, for example, if the person experiences concerning symptoms and seeks help, or from incidental findings from other investigations. On the other hand, they acknowledged that the risk of recurrence varies between individuals and that some people are at higher risk of recurrence than others. In these higher risk groups, the risk of recurrence may be higher initially and then reduce over time so that some ongoing follow-up is likely to be beneficial, but this benefit may decrease over time as their risk of recurrence decreases. The committee noted the benefit of early recurrence detection when the person is at performance status 0 or 1 as this is when systemic treatment is more likely to have a beneficial impact and that it is current practice to have a period of follow-up for people who have been treated for RCC. Moreover, early detection could improve a person's quality of life by identifying a potentially painful and symptomatic recurrence sooner, and in the committee's experience people who have been treated for RCC would feel very anxious if they were discharged without any follow-up period. Therefore, whilst the committee acknowledged the limited evidence, they agreed that it is still important to follow up people who have completed treatment for localised or locally advanced RCC for a defined amount of time and made a recommendation for follow-up to be offered to these people after they have completed treatment.

The committee were aware that there is variation in practice around the follow-up approaches across the UK. Due to the lack of evidence, they used their knowledge and experience to agree what a follow-up protocol should entail and agreed that as part of the follow-up approach, imaging should be offered at regular intervals to detect recurrence. In their experience, cross-sectional imaging is used in practice, and this is mainly contrast-enhanced CT (CECT) imaging unless there is a contraindication to the contrast medium. The committee had already looked at evidence for the diagnostic accuracy of CECT during diagnosis (see evidence review I1 on CT and MRI for diagnosing renal lesions) and had recommended using it at that stage in the pathway. They agreed that it would be similarly diagnostically useful during follow-up. The committee emphasised that conventional imaging such as ultrasound and x-ray is not usually used in practice for follow-up in the UK and that this is also reflected in international guidelines. They discussed the harms of higher radiation exposure with CT imaging compared to conventional methods but noted the need to balance these harms with CT's increased ability to detect a recurrence. They also noted that ad hoc CT scans or CT scans for other reasons such as non-cancer related symptoms and accidents may pick up recurrence outside of regular follow-up. Taking these points into account, the committee recommended CT imaging (with contrast) of the chest, abdomen and pelvis at regular intervals to detect recurrence. The committee were aware of other relevant NICE guidance and cross referred to them: NICE diagnostics guidance on point-of-care creatinine devices to assess kidney function before CT imaging with intravenous contrast and NICE guideline on Acute kidney injury on assessing risk factors in adults having iodine-based contrast media and how to prevent kidney injury in this population.

The committee acknowledged that in some cases MRI may be more appropriate than contrast-enhanced CT to detect recurrence. The committee had previously looked at the diagnostic accuracy of MRI for diagnosing renal lesions (as part of evidence review I1) and agreed that it would be similarly diagnostically useful during follow-up:

- If radiation exposure should be reduced: the committee recommended that follow-up using MRI (with or without contrast) of the abdomen and pelvis and CT (without contrast) of the chest should be offered. They noted that in some situations, for example during pregnancy, the risks and benefits of CT, even without contrast, would need to be carefully assessed to determine whether it should be carried out.

- If the person cannot have CT contrast: some people have allergies to the contrast agent used in CT. In these cases, MRI of the abdomen and pelvis, combined with CT (without contrast) of the chest may be suitable. The committee noted that an alternative to this, especially where MRI may not be easily accessible, could be CT (without contrast) of the chest, abdomen and pelvis.

The committee discussed the frequency of imaging and agreed that this should be based on the individual's risk of recurrence and that this would be calculated using a risk prediction tool where a suitable one is available. They had looked at the available risk prediction tools as part of a separate evidence review (evidence review L: risk prediction tools for localised and locally advanced renal cell carcinoma) and made recommendations on tools that could be used to calculate the risk of recurrence for people who had been treated for clear cell RCC or papillary RCC. This enables people to be placed into 1 of 3 risk groups- low, intermediate or high risk of recurrence.

There was no evidence identified as part of this review that could be used to determine the most effective frequency of imaging. The committee were aware of the European Association of Urology (EAU) guideline for RCC recommendations around follow-up and noted that the proposed follow-up schedule is based on expert consensus. The committee highlighted that the recently developed guidance (Getting It Right First Time (GIRFT) guide Urology: Towards better care for patients with kidney cancer), which is produced by the NHS, suggests a minimum acceptable frequency of imaging that this is based on a synthesis of other international guidelines (National Comprehensive Cancer Network, American Urological Association, Canadian Urological Association and European Association of Urology (EAU)). The committee agreed to align with this risk-stratified schedule for consistency and that this should be used to determine the minimum follow-up schedule for an individual using their calculated risk of recurrence. However, they agreed that changes should be made to the schedule if more frequent imaging is needed based on clinical and pathological characteristics.

The committee highlighted some specific groups whose risk status may not be possible to calculate according to the recommendations in the guideline section on 'risk prediction tools for localised and locally advanced RCC' (see evidence review K for more details):

- Where risk assessment is not possible: In some cases, an accurate risk assessment is not possible, for example if the person has not had a nephrectomy and so any pathology sample is limited to that from a biopsy (if they had SABR or thermal ablation). For these people, the committee recommended the use of the intermediate risk status follow-up schedule because they agreed that it should be more frequent than those known to be low risk, and this aligns with GIRFT.

- For people with chromophobe RCC: the committee agreed that if the person has been treated for chromophobe RCC, where there are no useful tools recommended by the committee for predicting risk of recurrence (see evidence review K), a low-risk status is a more suitable starting point because of the lower risk of recurrence associated with this subtype of RCC. Whilst the Leibovich 2018 tool was not recommended by the

committee, it uses clinical and pathological characteristics, such as the presence of fat invasion, sarcomatoid differentiation or nodal involvement to categorise risk of progression for chromophobe RCC. The committee agreed that the presence of these characteristics may also increase the risk of recurrence and therefore could be used to determine the risk level schedule being used following treatment for chromophobe RCC. They made a recommendation to reflect the different risk level status to be used following treatment for chromophobe RCC, with the absence of any of these characteristics being associated with low risk, the presence of fat invasion being associated with intermediate risk and the presence of sarcomatoid differentiation or nodal involvement suggesting that a high risk follow up schedule would be appropriate.

- People with a positive surgical margin: The committee highlighted that people with a positive surgical margin after partial nephrectomy may require a different follow-up schedule and agreed to align with GIRFT. They recommended that these people should have their risk level increased by one risk category. So, for example, if the person was assigned to the low-risk category for clear cell RCC recurrence using a risk tool, but had a positive surgical margin, they would move to the intermediate-risk category for follow-up.

The committee agreed that changes should be made to all follow-up schedules if more frequent imaging is needed based on clinical and pathological characteristics.

Patient impact and information to provide during follow-up

The committee discussed the importance of including people treated for RCC in decisions about the frequency of imaging and follow-up duration. They recognised that the end of treatment can be a stressful time for people who have had RCC and that they are often very worried about recurrence at least initially. However, they also acknowledged the impact that long-term follow-up can have on a person's mental well-being. They noted that reducing imaging frequency and follow-up duration, where appropriate, may be welcomed by some people but that others may find regular follow-up reassuring. The committee highlighted the importance of following recommendations in NICE's shared decision making guideline in these situations during these discussions. The committee were aware a new tool currently being developed, Predict Kidney tool, which could prove useful in the future. This tool aims to improve the communication of risk by providing a personalised risk assessment of cancer recurrence and death from other causes, presented in both numerical and visual formats.

The committee agreed that after the discussion about the follow-up schedule with the healthcare professional, it is important to provide the person who is being followed up with information about their imaging schedule, the team responsible for managing the follow-up (secondary care team) and the expected duration of follow-up for them to refer to. The committee therefore recommended that people who have been treated for RCC have a written personalised care plan including this information and details of a designated healthcare professional who is their point of contact and examples of when they should contact them, such as if they have symptoms that could indicate recurrence or metastases such as blood in their urine or persistent abdominal pain.

The committee included a cross reference to sections 7.2 and 3.9 of Getting It Right First Time (GIRFT) guide Urology: Towards better care for patients with kidney cancer for an example of what to include in a follow-up letter and information on patient support during follow-up, principles for good communication and information to communicate to patients.

Recurrence or development of metastases

Where recurrence or metastases are suspected, the committee recommended that further imaging or biopsy or both are carried out where needed to confirm diagnosis and the extent of any disease spread, to inform future management. Where recurrence or metastases is confirmed, the committee agreed that people would require treatment based on their diagnosis. However, this guideline did not look at the treatment of recurrences. The committee agreed that there are differences in treating a newly diagnosed RCC compared to a recurrence and so they did not cross refer to the management sections of the guideline for localised and locally advanced RCC. In contrast, they agreed that the section on treating metastatic RCC was relevant if the person developed metastases and included a cross reference to it.

Discharge

The committee noted that no evidence was identified to inform discussions about when people should be discharged from follow-up. They highlighted that agreeing on the point of discharge requires careful consideration of the benefits and harms of prolonging a follow-up schedule. The committee discussed the importance of balancing risk of recurrence in people treated with kidney cancer with risk of death from other comorbidities and whether they would benefit from treatment. They referred to a study by Stewart-Merrill et al. (2015) which showed no added clinical benefit to the individual of continuing with follow-up after the point at which the risk of death from something other than RCC exceeded the risk of recurrence.

Due to the lack of evidence, the committee referred to the GIRFT guideline and EAU guideline for RCC in addition to using their clinical expertise to reach a consensus. They agreed that where treatment for RCC recurrence or metastasis, if developed in the future, ceases to be an option then the person can usually be discharged from follow-up. The committee noted that the person may still be able to have other treatments to manage symptoms of RCC recurrence or metastasis should they arise, but these would be managed separately.

The committee noted that, while some people consider follow-up to be reassuring, others may find discharge to be a relief. They therefore agreed that clinicians should be encouraged to discharge people after a reasonable duration of follow-up where there is no sign of recurrence after a recent scan, and the individual has been fully informed about the process and agrees to being discharged. For people at low risk of recurrence, if there are no signs of recurrence or metastases on the 5-year scan they agreed that it would be appropriate to discharge them at this point because their risk of having a recurrence or metastases after this time is low. For people at intermediate or high risk they agreed that there should a discussion with the person about whether to continue follow-up imaging if there is no sign of recurrence or metastases after the scan at 5 years, with the expectations that follow up would continue. This decision should include consideration of their individual characteristics, including age, comorbidities and general fitness. They noted that people with intermediate or high risk of recurrence may have an initial higher risk of recurrence early on which sharply declines over time (while remaining higher than that in the low-risk group). If follow-up is continued, then a scan every 2 years is appropriate with a discussion about possible discharge to follow each time the scan results are reviewed and there is no sign of recurrence or metastases. The committee also discussed setting a potential time limit for discharging people with intermediate or high risk of recurrence who are followed up for longer than 5 years and agreed that if there is no recurrence or metastases, follow-up could be discontinued after 10 years unless there is a specific reason not to do this. They made a

recommendation to reflect these points. The committee also recommended that when being discharged from follow-up, the person should be given an explanation about why they are being discharged, told that primary care is their main point of contact and given examples of symptoms that could indicate recurrence or metastases that the person should contact primary care about (such as if they have blood in their urine or persistent abdominal pain).

1.1.12.4 Cost effectiveness and resource use

No cost effectiveness studies were identified in a search of the published literature. An original economic model was developed to address this review question, as it was considered to be an economic priority due to the likely high resource impact given the large population size and costs.

The strategies evaluated in the cost-effectiveness analysis were based on those for which there was effectiveness evidence from the clinical review. The main source of effectiveness evidence for follow-up strategies was from the RECUR database (Dabestani et al. 2019). Follow-up protocols used in practice are often risk stratified, with people assessed as being at low risk of recurrence requiring fewer scans than people assessed as being at high risk. In RECUR, the low-risk group had a cumulative 5-year risk of 3.8% for curable and 3.4% for incurable recurrences (7.2% overall), and the high-risk group had a 5-year risk of 18.79% for curable and 42.81% for incurable recurrences (61.6% overall). Therefore, the overall cost and cost effectiveness of imaging varies by risk group.

The imaging strategies compared in RECUR were a “high proportion of cross-sectional imaging” strategy versus a “low proportion of cross-sectional imaging” strategy, and a “low frequency of scans” strategy versus a “high frequency of scans” strategy over a median follow-up of 61.9 (IQR: 51.9-74.2) months (Dabestani et al. 2019). These imaging strategies were considered to be relatively loosely defined, and so it was not possible to evaluate specific strategies, such as around which imaging modality to use, the duration of follow-up or specific frequencies per year. As such, the economic model can indicate what type of imaging strategy is likely to be cost effective, rather than any specific strategy. There was also no information about the optimal duration of monitoring. The committee wished to consider a threshold analysis to determine the maximum number of scans in each risk group for a strategy to be cost effective. However, it was not possible to incorporate the analysis because the more precise relationship between scan frequency and scan type and effectiveness is not known.

The committee explained that motivation for earlier detection is treatment at the earliest possible stage of recurrence. Detecting non-symptomatic lesion was considered a proxy measure for early detection of lesions in the economic analysis, that is, detecting recurrence before symptoms develop. A research objective in the RECUR study was to identify recurrences that had curative potential, and an analysis of RECUR data supports a survival benefit for non-symptomatic lesion compared to symptomatic lesion. They are also associated with a benefit to a person’s quality of life.

The committee had concerns with the quality of the effectiveness evidence that was used to inform the economic model, which meant that the cost effectiveness results were also uncertain. The estimated probability of a detected lesion being non-symptomatic was not statistically significant, and it appears there may be an error in the RECUR publication for this outcome due to inconsistencies in how it was reported. The effectiveness evidence also appeared to be counter intuitive in the high-risk group. For example, the probability that a

recurrence detected by a high CSI strategy is non-symptomatic was lower than the low CSI strategy, which is counter to expectations given the greater accuracy of CSI. The committee suggested that this was because people in the high-risk group are more likely to require additional non-CSI scans (which are easier to access) beyond their follow-up protocol if recurrence is suspected. In this case, the total number of CSI scans remains as per the protocol, but the total non-CSI scans increases. This results in a low CSI strategy with a higher total number of scans but similar numbers of CSI scans to the high CSI strategy, which is more likely to detect early (non-symptomatic) recurrences.

The committee discussed the results of the cost-effectiveness analysis. The high CSI and high IF strategies were cost effective in the low- and intermediate-risk groups, with ICERs below the £20,000 threshold. In the high-risk group, the high CSI strategy is not cost effective as it was more costly and less effective than the low CSI strategy, and the high IF strategy might be cost effective with an ICER between £20,000 and £30,000 per QALY. Generally, there must be greater certainty in ICERs that are estimated within this range in order for the strategy to be considered for adoption, as the impact of the adoption of the strategy on NHS resources increases. The unexpected result for the high-CSI strategy was considered likely to be due to the issues with the underlying effectiveness evidence rather than any actual difference in effectiveness in this risk group, as the effectiveness evidence counterintuitively predicted a higher likelihood of detecting non-symptomatic recurrences in the low CSI strategy compared to the high CSI strategy in this study.

The total costs of each strategy were driven by the cost of imaging. The differences in outcomes (QALYs) were relatively small, with the majority of QALYs in the disease-free health state. In both analyses in all risk groups, the most influential parameter was the probability of being non-symptomatic, and changes in this parameter were the only scenarios where the conclusion of the economic analysis could change (i.e. an alternative strategy being cost effective).

The committee were presented with the unit costs of different resources used to assess people during follow-up. In addition to the scan, regular blood testing recommended by the committee would be routinely undertaken and is relatively inexpensive. People should also receive estimated glomerular filtration rate (eGFR) creatinine testing to detect and monitor any renal insufficiency and the risk of deterioration that might need separate management. Based on the GIRFT guidelines which recommend a minimum number of CT scans, the total 10-year cost of follow-up for a person who does not experience a recurrence (at which point, they will transition out of routine follow-up onto recurrence management care) ranges from £566 in the low-risk group to £1,886 in the high-risk group.

Given the uncertainty in the results of the economic analysis due to the associated uncertainty in the effectiveness evidence, the committee elected to recommend considering a minimum imaging schedule based on the existing GIRFT guidelines, noting that the economic analysis supported the use of cross-sectional imaging with contrast-enhanced CT (CECT) of the chest, abdomen and pelvis, at regular intervals. These were developed by expert consensus given the lack of data and are already used in practice in many centres in the UK. The recommendations are expected to standardise follow-up schedules and duration. Imaging frequency may increase in some centres and decrease in others; while resource use would increase with more frequent imaging, this could lead to earlier detection of recurrence, thus potentially reducing the need for more complex and costly treatments later on.

There was no evidence on follow-up duration or when to discharge someone. The committee agreed that clinicians sometimes think that keeping people on follow-up regimens for long periods of time is simpler than discharging them. Identifying when discharge is appropriate for the person is important as many people will find prolonged monitoring to be stressful. Monitoring for longer than necessary (i.e. when the person is at low risk of further recurrence) is not a good use of resources, and so recommendations to encourage more appropriate discharge may also lead to reductions in resource use by some people being discharged sooner.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.11.1 – 1.11.19 and the research recommendation on follow-up strategies for localised or locally advanced RCC.

1.1.14 References – included studies

1.1.14.1 Effectiveness

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1.1.14.2 Economic

None

1.1.15 References – other

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Leibovich BC, Blute ML, Cheville JC, et al. (2003). Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer 97(7):1663-71

Zisman A, Pantuck AJ, Dorey F, et al. (2001). Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol 19(6):1649-57

Appendices

Appendix A – Review protocols

Effectiveness review protocol

ID	Field	Content
1.	Review title	Review of follow-up strategies for monitoring any long-term consequences of treatment and early detection of disease progression in adults who have been treated for localised or locally advanced RCC
2.	Review question	For adults who have had treatment for localised or locally advanced RCC, what are the most clinically and cost-effective risk-stratified* follow-up strategies (based on method, duration, and frequency)? * risk refers to risk of recurrence or death
3.	Objective	To evaluate and compare the clinical effectiveness and cost-effectiveness of different follow-up strategies (e.g. different methods, duration, and frequency) for monitoring any long-term consequences of treatment and early detection of disease progression in adults who have been treated for localised or locally advanced RCC and who have been stratified into risk groups based on their risk of recurrence or death.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos For the economics review the following databases will be searched: • Embase • MEDLINE ALL • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA

		Database functionality will be used, where available, to exclude: • Non-OECD countries • Animal studies • Conference abstracts and posters • Registry entries for ongoing clinical trials or those that contain no results • Theses and dissertations • Papers not published in the English language • Search filters and classifiers • The following standard NICE filters will be used to limit results by study type: cost effectiveness studies / cost utility studies/ systematic reviews / randomised controlled trials and observational studies. • The full search strategies for all databases will be published in the final review.
5.	Condition or domain being studied	Localised or locally advanced RCC
6.	Population	Adults (18 years or over) who have been treated for localised or locally advanced RCC Diagnosis of localised and locally advanced RCC confirmed according to the clinical or pathological TNM classification. Treatment for RCC includes surgical and non-surgical interventions. Surgical interventions can be given with or without systemic anti-cancer therapy (SACT) delivered as a neoadjuvant or adjuvant treatment. Exclusion: • Adults with metastatic disease
7.	Intervention	Risk-stratified* follow-up protocols which might include: • Frequency of follow-up • Method of follow-up (e.g., type of imaging) • Duration of follow-up * risk refers to risk of recurrence or death. A tiered approach will be taken for this work:

		1. Follow-up strategies using risk stratified models that have been judged to be clinically useful (have good discrimination) by the committee in the review on prognosis risk tools will be included. 2. If studies using these models are not available, then any risk stratified follow-up strategy will be included.
8.	Comparator	Different risk stratified follow-up protocols compared to each other. (The protocols may differ in terms of follow-up duration, frequency and types of imaging/ tests carried out.)
9.	Types of study to be included	Systematic reviews of RCTs and RCTs. If RCTs are not available, then systematic reviews of non-randomised comparative studies and primary non-randomised comparative studies will be included. These are expected to include respective cohort studies based on registry data (such as studies using RECUR). Where good quality systematic reviews are identified, these may be used completely or as a source of references, depending on applicability.
10.	Other exclusion criteria	• Abstracts, conference presentations and theses • Non-human studies • Non-English language studies
11.	Context	There is currently no national guideline in the UK on the diagnosis and treatment of kidney cancer and audit data indicates variation in the clinical practice within NHS. Furthermore, there is no consensus on follow-up strategies after localised or locally advanced RCC treatment. Follow-up is important for early detection of disease recurrence and to evaluate long-term sequelae, such as impaired renal function, end-stage renal disease and cardiovascular events. Follow-up may vary depending on an individual's risk of progression. Following curative treatment for RCC, up to 30% of patients develop tumour recurrence. Prognostic scores are essential to guide individualised surveillance protocols, patient counselling, and potentially to guide therapy in a risk-stratified follow-up approach. Therefore, there is a need to identify which risk-stratified

		follow-up strategies after localised or locally advanced RCC treatment are most effective in detecting recurrence and improving outcomes for these patients.

12.	Outcomes	• Survival
		  ○ Disease-free survival, including cancer-free survival (time to event data)
		  ○ Overall survival (time to event data)
		Some studies may report death or mortality instead. These will be extracted as proxy outcomes where OS is unavailable (dichotomous data).
		• Cancer specific survival (time to event data)
		If cancer specific survival is not reported, then cancer specific mortality (dichotomous data) will be extracted instead where available.
		
		• Local recurrence (dichotomous data)
		• Distant recurrence (dichotomous data)
		• People with recurrence who require systemic treatment (dichotomous data)
		• People with recurrence who are suitable for curative treatment (dichotomous data)
		• People with recurrence who go on to have surveillance (dichotomous data)
		
		• Quality of life using:
		  ○ EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30; dichotomous or continuous data)
		  ○ EuroQol-5 dimensions (EQ-5D; dichotomous or continuous data)
		• Long term consequences of treatment:
		  ○ renal function impairment reported as glomerular filtration rate (eGFR; dichotomous or continuous data)
		  ○ cardiovascular events (dichotomous data)
		
		Minimal important differences
		Any statistically significant difference will be used for the following outcomes:
		  ○ Disease-free survival
		  ○ Overall survival
		  ○ Long-term consequences of treatment

		○ Quality of life using EORTC QLQ-C30 MIDs for the following quality of life measure was identified in the literature: EQ-5D: 0.08 for UK-based scores and 0.07 for VAS scores
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.2). Study investigators may be contacted for missing data where time and resources allow. This review may make use of the priority screening functionality within the EPPI-reviewer software. If priority screening is used, the following rules will be adopted to determine when to stop screening: • at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) will be screened • After this point, screening is only terminated if a threshold of 750 is met for a number of abstracts being screened without a single new include being identified. if sifting is terminated before the full database has been looked at additional checks will be carried out to ensure that relevant studies have not been missed.
14.	Risk of bias (quality) assessment	The risk of bias for RCTs will be assessed using the Cochrane Risk of Bias v.2.0 checklist and for systematic reviews, the Risk of Bias in Systematic Reviews (ROBIS) tool will be used, as described in Developing NICE guidelines: the manual The risk of bias for non-RCT studies will be assessed using the Cochrane Risk of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool, as described in Developing NICE guidelines: the manual
15.	Strategy for data synthesis	Where possible, meta-analyses will be conducted to combine the results of quantitative studies for each outcome. RCT and non-RCT data will be pooled separately.

		Where data can be disambiguated it will be separated into the subgroups identified in section 16 (below). Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. Continuous outcomes will be analysed as pooled mean differences (using the inverse variance method) unless multiple scales are used to measure the same factor. In these cases, standardised mean differences will be used instead. Where different studies present continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes will all converted to the same scale before meta-analysis is conducted on the mean differences. Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Hazard ratios will be pooled using the generic inverse-variance method. Adjusted, unadjusted and partially adjusted hazard ratios will be pooled. Sensitivity analysis will be carried out to look at the effect of removing partially and unadjusted studies. For survival outcomes, time-to-event data is preferred. Where this data is not available, relative risks will be calculated for proxy outcomes as described in section 12. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all outcomes, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions are met: • Significant between-study heterogeneity in methodology, population, intervention, or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

		GRADE will be used to assess the quality of the outcomes. Data from randomised controlled trials and non-randomised comparative trials will be initially rated as high quality where they come from: • RCTs and systematic reviews of RCTs (where individual studies have been quality assessed using Cochrane risk of bias) • non-randomised comparative trials and systematic reviews of non-randomised studies (where individual studies have been quality assessed using the ROBINS-I assessment tool) The quality of the evidence for each outcome will then be downgraded or not from this starting point based on the other GRADE domains. To assess imprecision, where there are no defined MIDs we will set the MID as the line of no effect for all outcomes (1.0 for dichotomous outcomes and 0 for continuous outcomes). A second decision threshold will be applied where the sample size is sufficiently small that it is not plausible any realistic effect size could have been detected. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias.
16.	Analysis of sub-groups	Where the data allows, subgroup analyses may be conducted to explore heterogeneity considering the following: • initial diagnosis • treatments received • age • Comorbidities • tumour size • renal function • performance status of the person • histological subtype • Healthcare setting.
17.	Type and method of review	X Intervention Diagnostic Prognostic Qualitative

<table>
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Service Delivery
Other (please specify)</td></tr>
<tr><td>18.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>19.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>20.</td><td>Anticipated or actual start date</td><td colspan="3">7th October 2024</td></tr>
<tr><td>21.</td><td>Anticipated completion date</td><td colspan="3">March 2026</td></tr>
<tr><td rowspan="7">22.</td><td rowspan="7">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td></td><td>X</td></tr>
<tr><td>Piloting of the study selection process</td><td></td><td>X</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td></td><td>X</td></tr>
<tr><td>Data extraction</td><td></td><td>X</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td></td><td>X</td></tr>
<tr><td>Data analysis</td><td></td><td>X</td></tr>
<tr><td>23.</td><td>Named contact</td><td colspan="3">Named contact
Centre for Guidelines, NICE

Named contact e-mail
kidneycancerguideline@nice.org.uk

Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE) and Guideline Development Team.</td></tr>
<tr><td>24.</td><td>Review team members</td><td colspan="3">From the Guideline Development Team:
• Steve Sharp, Technical adviser
• Sarah Boyce, Senior technical analyst
• Fernando Zanghelini, Technical analyst
• Lindsay Claxton, Health economics adviser
• Hannah Tebbs, Senior health economist
• Yuanyuan Zhang, Health economist
• Amy Finnegan, Senior Information specialist</td></tr>
<tr><td>25.</td><td>Funding sources/sponsor</td><td colspan="3">This systematic review is being completed by the Guideline Development Team which receives funding from NICE.</td></tr>
<tr><td>26.</td><td>Conflicts of interest</td><td colspan="3">All guideline committee members and anyone who has direct input into NICE guidelines</td></tr>
</table>

		(including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Kidney Cancer (GID-NG10398).
28.	Other registration details	None
29.	Reference/URL for published protocol	None
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
31.	Keywords	Localised renal cell carcinoma, thermal ablation, stereotactic ablative radiotherapy, active surveillance
32.	Details of existing review of same topic by same authors	Not applicable
33.	Current review status	Ongoing Completed but not published X Completed and published Completed, published and being updated Discontinued

34.	Additional information	None
35.	Details of final publication	www.nice.org.uk

Economic review protocol

ID	Field	Content
1.	Review title	For adults who have had treatment for localised or locally advanced RCC, what are the most clinically and cost-effective risk-stratified* follow-up strategies (based on method, duration, and frequency)? * risk refers to risk of recurrence or death
2.	Objective	To identify economic studies of different follow-up strategies (e.g. different methods, duration, and frequency) for monitoring any long-term consequences of treatment and early detection of disease progression in adults who have been treated for localised or locally advanced RCC and who have been stratified into risk groups based on their risk of recurrence or death
3.	Inclusion criteria	• Populations, interventions and comparators as specified in the effectiveness review protocol. • Relevant comparative economic study design: cost–utility analysis • Decision analytic model-based or within-trial economic analyses • OECD countries (except USA) • Healthcare and personal social services cost perspective • Studies published from 2010 – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs High-quality studies in line with the NICE reference case (recent UK NHS/PSS cost-utility analyses using the QALY as the measure of outcome) are the most applicable to NICE decision making. Not all studies meeting the inclusion criteria will therefore necessarily be used in decision-making - see Review strategy below for details.
4.	Exclusion criteria	• Conference posters or abstract only studies – these do not provide sufficient information for quality assessment. • Studies published before 2010 – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs • Studies from non-OECD countries or the USA – these are considered unlikely to be applicable to the UK NHS setting due to substantial differences in healthcare delivery and unit costs. • Non-comparative economic analyses including cost-of-illness studies. • Letters, editorials or commentaries, study protocols or reviews of economic evaluations (recent reviews will be ordered and the bibliographies will be checked for relevant individual economic studies, which will then be ordered and checked for eligibility). • Non-English language papers. • Studies considering exclusively intervention costs, e.g. medicine acquisition costs, without considering wider healthcare costs associated with the management of renal cell carcinoma. • Studies only focussing on productivity losses or gains.

5.	Search strategy	An economic study search will be undertaken covering the review question relating to follow-up and monitoring previously treated renal cell carcinoma using guideline population-specific terms and a health economic study filter. For search details see appendix B below. The following databases will be searched: • MEDLINE All, Ovid • Embase, Ovid • International HTA database, International Network of Agencies for Health Technology Assessment (INAHTA) • Econlit • NHS EED
6.	Review strategy	• Studies meeting the inclusion and exclusion criteria will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist in appendix H of Developing NICE guidelines: the manual. • The NICE economic evaluation checklist assesses: ○ Applicability to the NICE guideline decision making context with consideration of the NICE reference case relevant to the guideline. Recent UK studies that use the NICE reference case methods are the most applicable when considering cost effectiveness. ○ Methodological limitations. • The aim is to present the best available economic evidence to inform committee decision-making in the context of the guideline, the current UK NHS setting and NICE methods. Therefore, the health economist may not present all studies that meet inclusion criteria. If recent high quality, UK cost-utility analyses are available for a question, it is often not deemed informative to present studies that are less applicable or lower quality such as older UK analyses or analyses from other countries. A similar principle is deemed to apply more generally when considering applicability and methodological limitations. Some specific examples are given below: ○ If multiple versions of a model are available for the UK and other countries it is usually reasonable to only present the UK version. ○ If multiple versions of the same UK model are available, it is usually reasonable to present only the most recent. ○ If there has been a NICE MTA or guideline model that informs current NHS practice it is usually reasonable not to present older studies, unless they address a different subpopulation or other specific issue. ○ If a UK model that includes all interventions in the decision space is available it may be reasonable not to present studies that only include individual or fewer interventions, if the analysis is sufficiently applicable and of good methodological quality. • Quality and relevance of effectiveness data used in the economic analysis: the more closely the clinical effectiveness data used in the economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. • Hierarchy of economic evaluation evidence based on quality assessment ○ 'Directly applicable' and 'Minor limitations' (only recent UK CUAs can get this rating). Usually presented and used in decision-making.

		○ Directly or partially applicable combined with minor or potentially serious limitations (other than 1). Discretion over whether these are presented and used in decision-making, depending on the availability of more relevant evidence. ○ 'Not applicable' or 'Very serious limitations'. Typically not presented and not used in decision-making. The health economist will make a decision based on the relative applicability and quality of the available evidence for each question, in discussion with the guideline committee if required. All decisions will be transparently reported in the evidence report. Studies that are presented to the committee and used in decision-making when formulating recommendations will be included in the summary tables and will have an evidence extraction. Other studies may not be presented to the committee in detail but will be listed, with the reason for not being presented to the committee and thus not used in decision-making being provided. Committee members can review and query the decision not to present studies with the health economist and will be provided with full details of these studies where requested.

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches. The MEDLINE strategies below were quality assured (QA) by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search strategy was based on the population terms used in review questions A, B, C, H1 and H2 (review A: surgical interventions for localised RCC, review B: non-surgical interventions for localised RCC, review C: nephrectomy or stereotactic ablative radiotherapy for locally advanced RCC, reviews H1 and H2: non-pharmacological management of advanced RCC) for this guideline. The population for review F (current review) was amended to only include localised, stage-2 and stage-3 terminology.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries

- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations
- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic reviews: identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

No date limits were applied, in adherence to the review protocol.

Search filters and classifiers

Effectiveness searches

Systematic reviews filters:

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Medical Research Methodology*,* 12(1), 51.

- In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.
- In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Randomised control trial filters:

> The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version:
>
> The standard NICE modifications were used: the MeSH heading *randomized controlled trial/*, which is equivalent *to randomized controlled trial.pt* was exploded to capture newer, narrower *terms equivalence trial/ and pragmatic clinical trial*. The free-text term *randomized.mp* was also changed to the (more inclusive) alternative *randomi?ed.mp.* to capture both UK and US spellings.
>
> Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.
>
> The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version:

Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Observational filter:

The terms used for observational studies are standard NICE practice that have been developed in house.

OECD countries filter:

The MEDLINE and Embase searches were limited to evidence from Organisation for Economic Co-operation and Development (OECD) member states using the validated NICE filter.

The OECD countries filters were used without modification:

Ayiku, L., Hudson, T., Williams, C., Levay, P., & Jacob, C. (2021). The NICE OECD countries' geographic search filters: Part 2 - Validation of the MEDLINE and Embase (Ovid) filters. *Journal of the Medical Library Association*, 109(4), 583–589.

Cost effectiveness searches

In line with the review protocol, the sensitive version of the validated NICE cost utility filter was used in the MEDLINE and Embase strategies without amendment.

Hubbard W et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Medical Research Methodology*, 22(1), 310.

Health state utility balanced filter was used without modification:

Arber, M et al (2017) Performance of Ovid MEDLINE search filters to identify health state utility studies. International Journal of Technology Assessment in Health Care 33(4):472-80

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

The population set for review F (current review) was focused on localised, locally advanced, stage 2 and stage 3 of the condition. Other stages were out of scope for review F (current review). Letters, historical articles, comments, editorials, news or case reports were not removed from the Medline strategy to retain a known paper of interest.

1 paper was manually added to the search results. The paper was identified by the committee as being relevant but was not retrieved by the database searches as the paper was not within the scope of the protocol for review F (current review).

Clinical searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	07/10/2024	Wiley	Issue 10 of 12, October 2024	93
Cochrane Database of Systematic Reviews (CDSR)	07/10/2024	Wiley	Issue 10 of 12, October 2024	2
Embase	07/10/2024	Ovid	1974 to 2024 October 04	2169
Epistemonikos	07/10/2024	Epistemonikos	n/a	172
MEDLINE ALL	07/10/2024	Ovid	1946 to October 04, 2024	2084

Re-run search results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	17/04/2025	Wiley	Issue 3 of 12, March 2025	90
Cochrane Database of Systematic	17/04/2025	Wiley	Issue 3 of 12, March 2025	2

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Reviews (CDSR)				
Embase	17/04/2025	Ovid	1974 to 2025 April 16	2307
Epistemonikos	17/04/2025	Epistemonikos	n/a	209
MEDLINE ALL	17/04/2025	Ovid	1946 to April 16, 2025	2148

No date limits were applied to the rerun searches due to technical issues with OVID. The duplication of records was managed in EPPI Reviewer 5.

Search strategy history

Database name: Cochrane CENTRAL register of Controlled Trials (CDSR) and Cochrane Database of systematic reviews (CDSR)

Searches
#1 MeSH descriptor: [Kidney Neoplasms] explode all trees 1998
#2 (local* or stage-2 or stage-3 or stage-II or stage-III):ti,ab 126741
#3 #1 and #2 254
#4 ((local* or stage-2 stage-3 or stage-II or stage-III) NEAR/3 (Kidney* NEAR/2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumour* or tumor* or mass or metastat* or malignan* or sarcoma* or parenchyma*))):ti,ab 24
#5 ((local* or stage-2 stage-3 or stage-II or stage-III) NEAR/3 (collecting-duct* NEAR/2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumour* or tumor* or mass or metastat* or malignan* or sarcoma* or parenchyma*))):ti,ab 0
#6 ((local* or stage-2 stage-3 or stage-II or stage-III) NEAR/3 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumour* or renal-tumor* or grawitz-tumour* or grawitz-tumor* or hypernephroma* or nephrocarcinoma*)):ti,ab 158
#7 ((local* or stage-2 stage-3 or stage-II or stage-III) NEAR/3 (Kidney* NEAR/2 (Transitional-cell* or cell or urothelial* or duct or advanc*) NEAR/2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumour* or tumor* or mass or metastat* or malignan* or sarcoma* or parenchyma*))):ti,ab 6
#8 {or #3-#7} 356
#9 MeSH descriptor: [Risk Assessment] this term only 13623
#10 ((follow* NEXT up*) or followup):ti,ab,kw 347636
#11 ((risk* or prognos* or detect*) NEAR/3 (surviv* or recur* or reoccur* or death* or mort* or progress* or long-term or consequen* or stratif* or model* or group* or score* or interval*)):ti,ab,kw 74299
#12 ((regular* or routin* or schedul* or frequen* or day* or week* or month* or annual* or year* or FU) NEAR/3 (appointment* or check-up* or monitor* or observ* or computed-tomograph* or CT or CTX or magnetic-resonanc* or MRI or contrast-enhanc* or unenhanc* or imaging* or ultrasound* or ultra-sound*)):ti,ab 53592
#13 ((activ* or watch* or schedul* or routin* or close* or recur* or regular* or ongoing* or on-going* or structur* or stratif*) NEAR/3 (surveillan* or wait* or monitor* or observ* or watch*)):ti,ab 26971

Searches
#14 conditional-survival:ti,ab,kw 44
#15 (risk* NEAR/2 (assess* or analy* or benefit* or classifi* or tool* or adjust* or evaluat* or categor* or system* or score* or level* or check* or group* or grade*)):ti,ab 42217
#16 {or #9-#15} 465059
#17 #8 and #16 in Cochrane Reviews 2
#18 #8 and #16 in Trials 172
#19 "conference":pt or (clinicaltrials or trialsearch):so 784063
#20 #18 not #19 93

Database name: Embase

Searches
1 (local* or stage-2 stage-3 or stage-II or stage-III).ti,ab. and exp kidney tumor/ (17606)
2 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (372)
3 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (collecting-duct* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (1)
4 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*)).ti,ab. (3638)
5 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (Kidney* adj2 (Transitional-cell* or cell or urothelial* or duct or advanc*) adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (37)
6 or/1-5 (17857)
7 risk assessment/ or follow up/ (2922399)
8 (follow*-up* or followup).ti,ab,kw. (2268077)
9 ((risk* or prognos* or detect*) adj3 (surviv* or recur* or reoccur* or death* or mort* or progress* or long-term or consequen* or stratif* or model* or group* or score* or interval*)).ti,ab,kw. (968974)
10 ((regular* or routin* or schedul* or frequen* or day* or week* or month* or annual* or year* or FU) adj3 (appointment* or check-up* or monitor* or observ* or computed-tomograph* or CT or CTX or magnetic-resonanc* or MRI or contrast-enhanc* or unenhanc* or imaging* or ultrasound* or ultra-sound*)).ti,ab. (500981)
11 ((activ* or watch* or schedul* or routin* or close* or recur* or regular* or ongoing* or on-going* or structur* or stratif*) adj3 (surveillan* or wait* or monitor* or observ* or watch*)).ti,ab. (400266)
12 conditional-survival.ti,ab,kw. (1065)
13 (risk* adj2 (assess* or analy* or benefit* or classifi* or tool* or adjust* or evaluat* or categor* or system* or score* or level* or check* or group* or grade*)).ti,ab. (662067)
14 or/7-13 (4977131)
15 6 and 14 (8178)
16 limit 15 to english language (7602)

Searches
17 nonhuman/ not (human/ and nonhuman/) (5543172)
18 16 not 17 (7563)
19 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1814431)
20 exp "organisation for economic co-operation and development"/ (3190)
21 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (3934633)
22 european union/ (32777)
23 developed country/ (36489)
24 or/20-23 (3970000)
25 19 not 24 (1652708)
26 18 not 25 (7363)
27 random:.tw. (2128008)
28 placebo:.mp. (546892)
29 double-blind:.tw. (256515)
30 or/27-29 (2413712)
31 (MEDLINE or pubmed).tw. (467495)
32 exp systematic review/ or systematic review.tw. (581500)

Searches
33 meta-analysis/ (332377)
34 intervention$.ti. (291146)
35 or/31-34 (1084322)
36 clinical study/ (167878)
37 observational study/ (395468)
38 exp cohort analysis/ (1226600)
39 exp comparative study/ (1760373)
40 (observational adj (study or studies)).tw. (288872)
41 ((follow up* or followup* or concurrent* or incidence* or population* or control*) adj3 (study* or studies* or analy* or observation* or design* or method* or research*)).ti,ab. (1609595)
42 Longitudinal study/ or Retrospective study/ or comparative study/ or Prospective study/ (3657212)
43 (longitudinal* or prospective* or retrospective* or cohort*).ti,ab. (4446368)
44 or/36-42 (6274041)
45 30 or 35 or 44 (8465898)
46 26 and 45 (3658)
47 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (6031587)
48 46 not 47 (2181)
49 48 not (letter or editorial).pt. (2169)

Database name: Epistemonikos

Searches
(title:(((local* OR stage-2 OR "stage 2" OR stage-II OR "stage II" OR stage-3 OR "stage 3" OR stage-III OR "stage III") AND (kidney* AND (cancer* OR carcinoma* OR carcinosarcoma* OR adenocarcino* OR neoplas* OR tumour* OR tumor* OR mass OR metastat* OR malignan* OR sarcoma* OR parenchyma*))) OR ((local* OR stage-2 OR "stage 2" OR stage-II OR "stage II" OR stage-3 OR "stage 3" OR stage-III OR "stage III") AND (collecting-duct* AND (cancer* OR carcinoma* OR carcinosarcoma* OR adenocarcino* OR neoplas* OR tumour* OR tumor* OR mass OR metastat* OR malignan* OR sarcoma* OR parenchyma*))) OR ((local* OR stage-2 OR "stage 2" OR stage-II OR "stage II" OR stage-3 OR "stage 3" OR stage-III OR "stage III") AND (renal-cell* OR rcc OR ccrcc OR renal-mass* OR renal-tumour* OR renal-tumor* OR grawitz-tumour* OR grawitz-tumor* OR hypernephroma* OR nephrocarcinoma*)) OR ((local* OR stage-2 OR "stage 2" OR stage-II OR "stage II" OR stage-3 OR "stage 3" OR stage-III OR "stage III") AND (kidney* AND (transitional-cell* OR cell OR urothelial* OR duct OR advanc*) AND (cancer* OR carcinoma* OR carcinosarcoma* OR adenocarcino* OR neoplas* OR tumour* OR tumor* OR mass OR metastat* OR malignan* OR sarcoma* OR parenchyma*)))) OR abstract:(((local* OR stage-2 OR "stage 2" OR stage-II OR "stage II" OR stage-3 OR "stage 3" OR stage-III OR "stage III") AND (kidney* AND (cancer* OR carcinoma* OR carcinosarcoma* OR adenocarcino* OR neoplas* OR tumour* OR tumor* OR mass OR metastat* OR malignan* OR sarcoma* OR parenchyma*))) OR ((local* OR stage-2 OR "stage 2" OR stage-II OR "stage II" OR stage-3 OR "stage 3" OR stage-III OR "stage III") AND (collecting-duct* AND (cancer* OR carcinoma* OR carcinosarcoma* OR adenocarcino* OR neoplas* OR tumour* OR tumor* OR mass OR metastat* OR malignan* OR sarcoma* OR parenchyma*))) OR ((local* OR stage-2 OR "stage 2" OR stage-II OR "stage II" OR stage-3 OR "stage 3" OR stage-III OR "stage III") AND (renal-cell* OR rcc OR

Searches
ccrcc OR renal-mass* OR renal-tumour* OR renal-tumor* OR grawitz-tumour* OR grawitz-tumor* OR hypernephroma* OR nephrocarcinoma*)) OR ((local* OR stage-2 OR "stage 2" OR stage-II OR "stage II" OR stage-3 OR "stage 3" OR stage-III OR "stage III") AND (kidney* AND (transitional-cell* OR cell OR urothelial* OR duct OR advanc*) AND (cancer* OR carcinoma* OR carcinosarcoma* OR adenocarcino* OR neoplas* OR tumour* OR tumor* OR mass OR metastat* OR malignan* OR sarcoma* OR parenchyma*))))) AND (title:(((follow* AND up*) OR followup) OR ((risk* OR prognos* OR detect*) AND (surviv* OR recur* OR reoccur* OR death* OR mort* OR progress* OR long-term OR consequen* OR stratif* OR model* OR group* OR score* OR interval*)) OR ((regular* OR routin* OR schedul* OR frequen* OR day* OR week* OR month* OR annual* OR year* OR fu) AND (appointment* OR check-up* OR monitor* OR observ* OR computed-tomograph* OR ct OR ctx OR magnetic-resonanc* OR mri OR contrast-enhanc* OR unenhanc* OR imaging* OR ultrasound* OR ultra-sound*)) OR ((activ* OR watch* OR schedul* OR routin* OR close* OR recur* OR regular* OR ongoing* OR on-going* OR structur* OR stratif*) AND (surveillan* OR wait* OR monitor* OR observ* OR watch*)) OR conditional-survival OR (risk* AND (assess* OR analy* OR benefit* OR classifi* OR tool* OR adjust* OR evaluat* OR categor* OR system* OR score* OR level* OR check* OR group* OR grade*))) OR abstract:(((follow* AND up*) OR followup) OR ((risk* OR prognos* OR detect*) AND (surviv* OR recur* OR reoccur* OR death* OR mort* OR progress* OR long-term OR consequen* OR stratif* OR model* OR group* OR score* OR interval*)) OR ((regular* OR routin* OR schedul* OR frequen* OR day* OR week* OR month* OR annual* OR year* OR fu) AND (appointment* OR check-up* OR monitor* OR observ* OR computed-tomograph* OR ct OR ctx OR magnetic-resonanc* OR mri OR contrast-enhanc* OR unenhanc* OR imaging* OR ultrasound* OR ultra-sound*)) OR ((activ* OR watch* OR schedul* OR routin* OR close* OR recur* OR regular* OR ongoing* OR on-going* OR structur* OR stratif*) AND (surveillan* OR wait* OR monitor* OR observ* OR watch*)) OR conditional-survival OR (risk* AND (assess* OR analy* OR benefit* OR classifi* OR tool* OR adjust* OR evaluat* OR categor* OR system* OR score* OR level* OR check* OR group* OR grade*))))
Limited to Systematic reviews: 172

Database name: Medline ALL

Searches
1 (local* or stage-2 or stage-3 or stage-II or stage-III).ti,ab. and exp Kidney Neoplasms/ (8076)
2 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (207)
3 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (collecting-duct* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (1)
4 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*)).ti,ab. (2096)
5 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (Kidney* adj2 (Transitional-cell* or cell or urothelial* or duct or advanc*) adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (22)
6 or/1-5 (8512)
7 Risk Assessment/ (318137)

Searches
8 (follow*-up* or followup).ti,ab,kw. (1413895)
9 ((risk* or prognos* or detect*) adj3 (surviv* or recur* or reoccur* or death* or mort* or progress* or long-term or consequen* or stratif* or model* or group* or score* or interval*)).ti,ab,kw. (630945)
10 ((regular* or routin* or schedul* or frequen* or day* or week* or month* or annual* or year* or FU) adj3 (appointment* or check-up* or monitor* or observ* or computed-tomograph* or CT or CTX or magnetic-resonanc* or MRI or contrast-enhanc* or unenhanc* or imaging* or ultrasound* or ultra-sound*)).ti,ab. (322327)
11 ((activ* or watch* or schedul* or routin* or close* or recur* or regular* or ongoing* or on-going* or structur* or stratif*) adj3 (surveillan* or wait* or monitor* or observ* or watch*)).ti,ab. (291373)
12 conditional-survival.ti,ab,kw. (645)
13 (risk* adj2 (assess* or analy* or benefit* or classifi* or tool* or adjust* or evaluat* or categor* or system* or score* or level* or check* or group* or grade*)).tw. (456261)
14 or/7-13 (2825603)
15 6 and 14 (3379)
16 limit 15 to english language (2989)
17 animals/ not humans/ (5230472)
18 16 not 17 (2976)
19 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ (1373543)
20 exp "organisation for economic co-operation and development"/ (632)
21 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or

Searches
exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3598727)
22 european union/ (18204)
23 developed countries/ (21641)
24 or/20-23 (3615276)
25 19 not 24 (1281808)
26 18 not 25 (2920)
27 exp Randomized Controlled Trial/ (624615)
28 randomi?ed.mp. (1144999)
29 placebo.mp. (260690)
30 or/27-29 (1213521)
31 (MEDLINE or pubmed).tw. (377205)
32 systematic review.tw. (318417)
33 systematic review.pt. (274860)
34 meta-analysis.pt. (209300)
35 intervention$.ti. (221801)
36 or/31-35 (778494)
37 Observational Studies as Topic/ (10074)
38 Observational Study/ or exp Cohort Studies/ (2715828)
39 Comparative Study.pt. (1928942)
40 (observational adj (study or studies)).tw. (186451)
41 ((follow up* or followup* or concurrent* or incidence* or population*) adj3 (study* or studies* or analy* or observation* or design* or method* or research*)).ti,ab. (516227)
42 (longitudinal* or prospective* or retrospective* or cohort*).ti,ab. (2806726)
43 or/37-42 (5674374)
44 30 or 36 or 43 (6854293)
45 26 and 44 (2087)
46 ("clinical conference" or congress* or overall* or consensus*).pt. or (conference* or proceeding*).jn. or (conference* not (video* or conference-call* or case* or charter* or declaration* or treaty* or treaties)).ti. (390212)
47 45 not 46 (2084)

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
EconLit	14/10/2024	OVID	1886 to October 03, 2024	1

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	14/10/2024	Ovid	1974 to October 11, 2024	97
International Health Technology Assessment Database from INAHTA	14/10/2024	https://database.inahta.org/	n/a	12
MEDLINE ALL	14/10/2024	Ovid	1946 to October 11, 2024	56
NHS EED	14/10/2024	CRD	n/a	4

Re-run search results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
EconLit	07/05/2025	OVID	1886 to May 01, 2025	1
Embase	07/05/2025	Ovid	1974 to 2024 May 06 2025	101
International Health Technology Assessment Database from INAHTA	07/05/2025	https://database.inahta.org/	n/a	12
MEDLINE ALL	07/05/2025	Ovid	1946 to May 06, 2025	56

Date limits were not applied to the rerun searches due to technical issues in OVID. Duplication of records was managed in EPPI Reviewer 5. NHS EED was not included in the rerun searches as the database only contains legacy information and is not updated.

Search strategy history

Database name: Econlit

Searches
1 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (0)
2 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (collecting-duct* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (0)
3 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*)).ti,ab. (1)
4 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (Kidney* adj2 (Transitional-cell* or cell or urothelial* or duct or advanc*) adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (0)
5 or/1-4 (1)
6 D81.cc. (16854)
7 (follow*-up* or followup).ti,ab,kw. (2526)
8 ((risk* or prognos* or detect*) adj3 (surviv* or recur* or reoccur* or death* or mort* or progress* or long-term or consequen* or stratif* or model* or group* or score* or interval*)).ti,ab,kw. (12711)
9 ((regular* or routin* or schedul* or frequen* or day* or week* or month* or annual* or year* or FU) adj3 (appointment* or check-up* or monitor* or observ* or computed-tomograph* or CT or CTX or magnetic-resonanc* or MRI or contrast-enhanc* or unenhanc* or imaging* or ultrasound* or ultra-sound*)).ti,ab. (4073)
10 ((activ* or watch* or schedul* or routin* or close* or recur* or regular* or ongoing* or on-going* or structur* or stratif*) adj3 (surveillan* or wait* or monitor* or observ* or watch*)).ti,ab. (4542)
11 conditional-survival.ti,ab,kw. (21)
12 (risk* adj2 (assess* or analy* or benefit* or classifi* or tool* or adjust* or evaluat* or categor* or system* or score* or level* or check* or group* or grade*)).tw. (20389)
13 or/6-12 (55615)
14 5 and 13 (1)

Database name: Embase

Searches
1 (local* or stage-2 stage-3 or stage-II or stage-III).ti,ab. and exp kidney tumor/ (17620)
2 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (373)
3 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (collecting-duct* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (1)

Searches
4 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*)).ti,ab. (3641)
5 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (Kidney* adj2 (Transitional-cell* or cell or urothelial* or duct or advanc*) adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (37)
6 or/1-5 (17871)
7 risk assessment/ or follow up/ (2927866)
8 (follow*-up* or followup).ti,ab,kw. (2272492)
9 ((risk* or prognos* or detect*) adj3 (surviv* or recur* or reoccur* or death* or mort* or progress* or long-term or consequen* or stratif* or model* or group* or score* or interval*)).ti,ab,kw. (971308)
10 ((regular* or routin* or schedul* or frequen* or day* or week* or month* or annual* or year* or FU) adj3 (appointment* or check-up* or monitor* or observ* or computed-tomograph* or CT or CTX or magnetic-resonanc* or MRI or contrast-enhanc* or unenhanc* or imaging* or ultrasound* or ultra-sound*)).ti,ab. (501800)
11 ((activ* or watch* or schedul* or routin* or close* or recur* or regular* or ongoing* or on-going* or structur* or stratif*) adj3 (surveillan* or wait* or monitor* or observ* or watch*)).ti,ab. (400842)
12 conditional-survival.ti,ab,kw. (1068)
13 (risk* adj2 (assess* or analy* or benefit* or classifi* or tool* or adjust* or evaluat* or categor* or system* or score* or level* or check* or group* or grade*)).ti,ab. (663516)
14 or/7-13 (4985782)
15 6 and 14 (8181)
16 limit 15 to english language (7605)
17 nonhuman/ not (human/ and nonhuman/) (5547106)
18 16 not 17 (7566)
19 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/

Searches
or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1816978)
20 exp "organisation for economic co-operation and development"/ (3203)
21 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (3938319)
22 european union/ (32819)
23 developed country/ (36502)
24 or/20-23 (3973726)
25 19 not 24 (1655067)
26 18 not 25 (7366)
27 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (6043582)
28 26 not 27 (4165)
29 cost utility analysis/ (13259)
30 quality adjusted life year/ (38588)
31 cost*.ti. (205265)
32 (cost* adj2 utilit*).tw. (13690)
33 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (414611)
34 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (71563)
35 (qualit* adj2 adjust* adj2 life*).tw. (29483)
36 QALY*.tw. (28891)
37 (incremental* adj2 cost*).tw. (30805)
38 ICER.tw. (14233)
39 utilities.tw. (16115)
40 markov*.tw. (42963)
41 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (77286)
42 ((utility or effective*) adj2 analys*).tw. (40691)
43 (willing* adj2 pay*).tw. (16167)
44 (EQ5D* or EQ-5D*).tw. (28742)
45 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (5915)
46 (european* adj2 quality adj3 ("5" or five)).tw. (1107)
47 or/29-46 (679904)

Searches
48 (qald$ or qale$ or qtime$).ti,ab,kf. (457)
49 (illness state$1 or health state$1).ti,ab,kf. (15823)
50 (hui or hui1 or hui2 or hui3).ti,ab,kf. (3450)
51 (multiattribute$ or multi attribute$).ti,ab,kf. (1714)
52 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (35019)
53 utilities.ti,ab,kf. (16352)
54 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (48491)
55 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (3812)
56 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (36260)
57 quality of life/ and ec.fs. (68993)
58 quality of life/ and (health adj3 status).ti,ab,kf. (22832)
59 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ (7304)
60 or/48-59 (226640)
61 Health economics/ (36828)
62 exp health care cost/ (359477)
63 exp Fee/ (45768)
64 exp Budget/ (35238)
65 Funding/ (82583)
66 budget*.ti,ab. (50445)
67 (economic* or pharmaco?economic*).ti. (81438)
68 (price* or pricing*).ti,ab. (78750)
69 (financ* or fee or fees).ti,ab. (252516)
70 (value adj2 (money or monetary)).ti,ab. (4389)
71 or/61-70 (840735)
72 28 and (47 or 60 or 71) (97)

Database name: International Health Technology Assessment Database from INAHTA

Searches
#1 ("kidney neoplasms"[mhe]) AND ((local* or "stage-2" or "stage-3" or "stage-ii" or "stage-iii")) 16
#2 ((local* or "stage-2" "stage-3" or "stage-ii" or "stage-iii") AND (kidney* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumour* or tumor* or mass or metastat* or malignan* or sarcoma* or parenchyma*))) 16
#3 (((local* or "stage-2" "stage-3" or "stage-ii" or "stage-iii") AND ("collecting-duct"* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumour* or tumor* or mass or metastat* or malignan* or sarcoma* or parenchyma*)))) 1
#4 ((local* or "stage-2" "stage-3" or "stage-ii" or "stage-iii") AND ("renal-cell"* or rcc or ccrcc or "renal-mass"* or "renal-tumour"* or "renal-tumor"* or "grawitz-tumour"* or "grawitz-tumor"* or hypernephroma* or nephrocarcinoma*)) 13

Searches
#5 (((local* or "stage-2" "stage-3" or "stage-ii" or "stage-iii") AND (kidney* AND ("transitional-cell"* or cell or urothelial* or duct or advanc*) AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumour* or tumor* or mass or metastat* or malignan* or sarcoma* or parenchyma*)))) 9
#6 #5 OR #4 OR #3 OR #2 OR #1 27
#7 "risk assessment"[mh] 150
#8 ((follow* AND up*) or followup) 671
#9 ((risk* or prognos* or detect*) AND (surviv* or recur* or reoccur* or death* or mort* or progress* or "long-term" or consequen* or stratif* or model* or group* or score* or interval*)) 2968
#10 ((regular* or routin* or schedul* or frequen* or day* or week* or month* or annual* or year* or fu) AND (appointment* or "check-up"* or monitor* or observ* or "computed-tomograph"* or ct or ctx or "magnetic-resonanc"* or mri or "contrast-enhanc"* or unenhanc* or imaging* or ultrasound* or "ultra-sound"*)) 1641
#11 ((activ* or watch* or schedul* or routin* or close* or recur* or regular* or ongoing* or "on-going"* or structur* or stratif*) AND (surveillan* or wait* or monitor* or observ* or watch*)) 1253
#12 "conditional-survival" 0
#13 (risk* AND (assess* or analy* or benefit* or classifi* or tool* or adjust* or evaluat* or categor* or system* or score* or level* or check* or group* or grade*)) 3206
#14 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 5240
#15 #14 AND #6 12

Database name: Medline ALL

Searches
1 (local* or stage-2 or stage-3 or stage-II or stage-III).ti,ab. and exp Kidney Neoplasms/ (8082)
2 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (208)
3 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (collecting-duct* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (1)

Searches
4 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*)).ti,ab. (2099)
5 ((local* or stage-2 stage-3 or stage-II or stage-III) adj3 (Kidney* adj2 (Transitional-cell* or cell or urothelial* or duct or advanc*) adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (22)
6 or/1-5 (8518)
7 Risk Assessment/ (318432)
8 (follow*-up* or followup).ti,ab,kw. (1415374)
9 ((risk* or prognos* or detect*) adj3 (surviv* or recur* or reoccur* or death* or mort* or progress* or long-term or consequen* or stratif* or model* or group* or score* or interval*)).ti,ab,kw. (631837)
10 ((regular* or routin* or schedul* or frequen* or day* or week* or month* or annual* or year* or FU) adj3 (appointment* or check-up* or monitor* or observ* or computed-tomograph* or CT or CTX or magnetic-resonanc* or MRI or contrast-enhanc* or unenhanc* or imaging* or ultrasound* or ultra-sound*)).ti,ab. (322624)
11 ((activ* or watch* or schedul* or routin* or close* or recur* or regular* or ongoing* or on-going* or structur* or stratif*) adj3 (surveillan* or wait* or monitor* or observ* or watch*)).ti,ab. (291648)
12 conditional-survival.ti,ab,kw. (645)
13 (risk* adj2 (assess* or analy* or benefit* or classifi* or tool* or adjust* or evaluat* or categor* or system* or score* or level* or check* or group* or grade*)).tw. (456989)
14 or/7-13 (2828789)
15 6 and 14 (3382)
16 limit 15 to english language (2992)
17 animals/ not humans/ (5232485)
18 16 not 17 (2979)
19 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/

Searches
or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ (1375157)
20 exp "organisation for economic co-operation and development"/ (633)
21 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3600771)
22 european union/ (18209)
23 developed countries/ (21644)
24 or/20-23 (3617327)
25 19 not 24 (1283374)
26 18 not 25 (2922)
27 cost utility analysis/ (95895)
28 quality adjusted life year/ (16929)
29 cost*.ti. (152862)
30 (cost* adj2 utilit*).tw. (8329)
31 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (301965)
32 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (51389)
33 (qualit* adj2 adjust* adj2 life*).tw. (19332)
34 QALY*.tw. (15691)
35 (incremental* adj2 cost*).tw. (18796)
36 ICER.tw. (6722)
37 utilities.tw. (10113)
38 markov*.tw. (34145)
39 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (57401)
40 ((utility or effective*) adj2 analys*).tw. (27112)
41 (willing* adj2 pay*).tw. (10914)
42 (EQ5D* or EQ-5D*).tw. (15051)
43 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4407)
44 (european* adj2 quality adj3 ("5" or five)).tw. (802)
45 or/27-44 (530597)
46 (qald$ or qale$ or qtime$).ti,ab,kf. (255)
47 (illness state$1 or health state$1).ti,ab,kf. (9068)
48 (hui or hui1 or hui2 or hui3).ti,ab,kf. (2142)
49 (multiattribute$ or multi attribute$).ti,ab,kf. (1514)

Searches
50 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (22201)
51 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (28301)
52 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (2564)
53 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (17041)
54 quality of life/ and ec.fs. (11086)
55 quality of life/ and (health adj3 status).ti,ab,kf. (12695)
56 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ (18138)
57 ((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. (60585)
58 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf. (5728)
59 *quality of life/ and (quality of life or qol).ti. (67943)
60 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf. (46446)
61 quality of life/ and health-related quality of life.ti,ab,kf. (49132)
62 models, economic/ (11339)
63 or/46-62 (218274)
64 Economics/ (27540)
65 Value of life/ (5832)
66 exp "Costs and Cost Analysis"/ (273704)
67 exp Economics, Hospital/ (26002)
68 exp Economics, Medical/ (14449)
69 Economics, Nursing/ (4013)
70 Economics, Pharmaceutical/ (3149)
71 exp "Fees and Charges"/ (31541)
72 exp Budgets/ (14265)
73 budget*.ti,ab. (38304)
74 cost*.ti. (152862)
75 (economic* or pharmaco?economic*).ti. (65445)
76 (price* or pricing*).ti,ab. (57892)
77 (financ* or fee or fees).ti,ab. (175922)
78 (value adj2 (money or monetary)).ti,ab. (3289)
79 or/64-78 (644265)
80 26 and (45 or 63 or 79) (56)

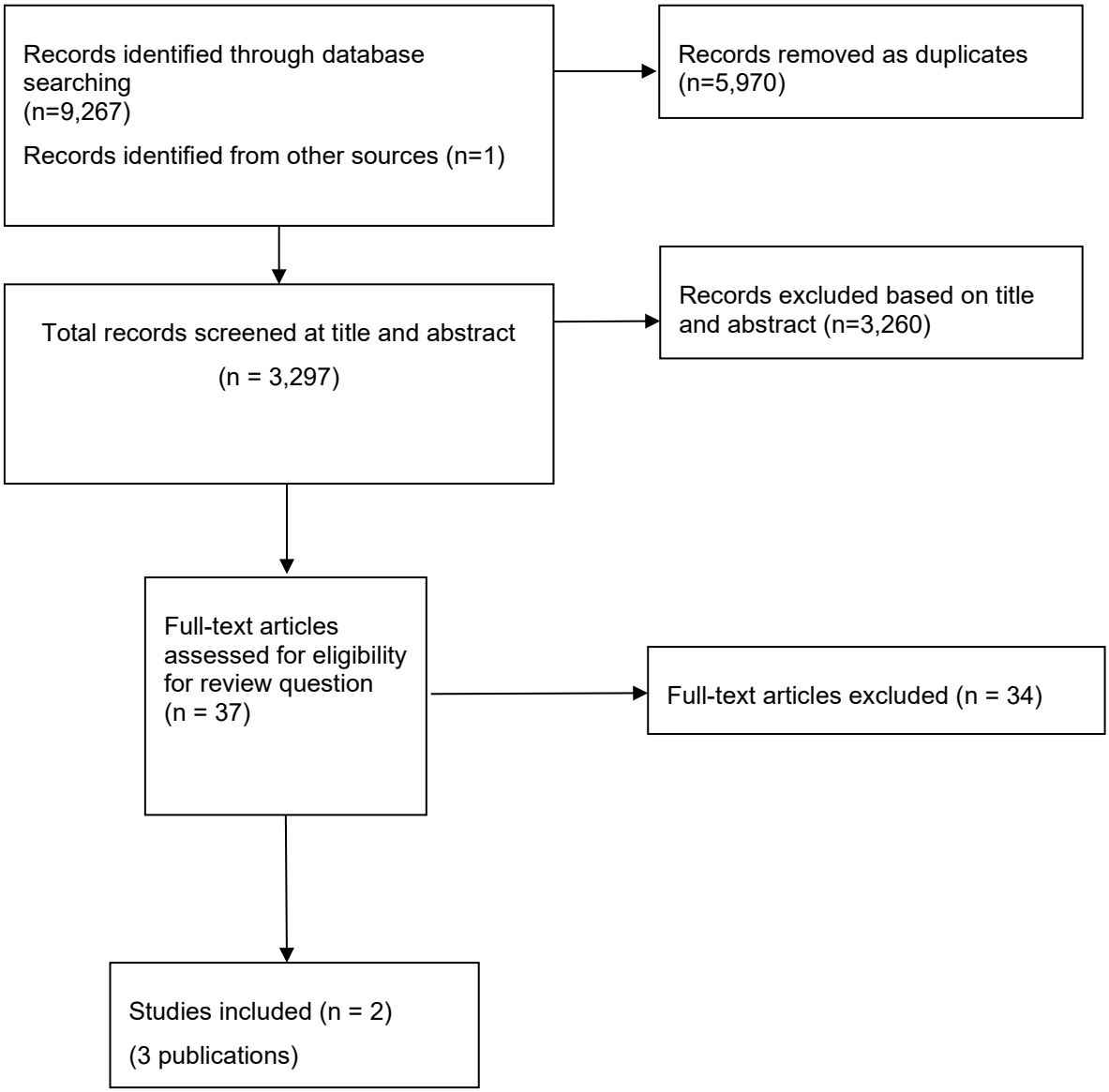
Database name: NHS EED

Searches

Line	Search	Hits
1	MESH DESCRIPTOR Kidney Neoplasms EXPLODE ALL TREES	201
2	(local* or stage-2 or stage-3 or stage-II or stage-III)	4804
3	#1 and #2	34
4	((local* or stage-2 stage-3 or stage-II or stage-III) NEAR3 (Kidney* NEAR2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumour* or tumor* or mass or metastat* or malignan* or sarcoma* or parenchyma*)))	1
5	((local* or stage-2 stage-3 or stage-II or stage-III) NEAR3 (collecting-duct* NEAR2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumour* or tumor* or mass or metastat* or malignan* or sarcoma* or parenchyma*)))	0
6	((local* or stage-2 stage-3 or stage-II or stage-III) NEAR3 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumour* or renal-tumor* or grawitz-tumour* or grawitz-tumor* or hypernephroma* or nephrocarcinoma*))	14
7	((local* or stage-2 stage-3 or stage-II or stage-III) NEAR3 (Kidney* NEAR2 (Transitional-cell* or cell or urothelial* or duct or advanc*) NEAR2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumour* or tumor* or mass or metastat* or malignan* or sarcoma* or parenchyma*)))	1
8	#3 or #4 or #5 or #6 or #7	35
9	MESH DESCRIPTOR Risk Assessment	2119
10	((follow* NEXT up*) or followup)	15980
11	((risk* or prognos* or detect*) NEAR3 (surviv* or recur* or reoccur* or death* or mort* or progress* or long-term or consequen* or stratif* or model* or group* or score* or interval*))	4055
12	((regular* or routin* or schedul* or frequen* or day* or week* or month* or annual* or year* or FU) NEAR3 (appointment* or check-up* or monitor* or observ* or computed-tomograph* or CT or CTX or magnetic-resonanc* or MRI or contrast-enhanc* or unenhanc* or imaging* or ultrasound* or ultra-sound*))	819
13	((activ* or watch* or schedul* or routin* or close* or recur* or regular* or ongoing* or on-going* or structur* or stratif*) NEAR3 (surveillan* or wait* or monitor* or observ* or watch*))	627
14	conditional-survival	0
15	(risk* NEAR2 (assess* or analy* or benefit* or classifi* or tool* or adjust* or evaluat* or categor* or system* or score* or level* or check* or group* or grade*))	4772
16	#9 or #10 or #11 or #12 or #13 or #14 or #15	21121
17	(#8 and #16) IN NHSEED	4

Appendix C – Effectiveness evidence study selection

Figure 4: PRISMA diagram



Appendix D – Effectiveness evidence

Dabestani, 2019a

Bibliographic Reference	Dabestani, Saeed; Beisland, Christian; Stewart, Grant D; Bensalah, Karim; Gudmundsson, Eirikur; Lam, Thomas B; Gietzmann, William; Zakikhani, Paimaun; Marconi, Lorenzo; Fernandez-Pello, Sergio; Monagas, Serenella; Williams, Samuel P; Powles, Thomas; Van Werkhoven, Erik; Meijer, Richard; Volpe, Alessandro; Staehler, Michael; Ljungberg, Borje; Bex, Axel; Increased use of cross-sectional imaging for follow-up does not improve post-recurrence survival of surgically treated initially localized R.C.C.: results from a European multicenter database (R.E.C.U.R.).; Scandinavian journal of urology; 2019; vol. 53 (no. 1); 14-20

Study details

Other publications associated with this study included in review	Dabestani et al. Intensive Imaging-based Follow-up of Surgically Treated Localised Renal Cell Carcinoma Does Not Improve Post-recurrence Survival: Results from a European Multicentre Database (RECUR).; European urology; 2019; vol. 75 (no. 2); 261-264
Study type	Retrospective cohort study
Study location	Eight European countries (Sweden, Iceland, United Kingdom, Norway, The Netherlands, Portugal, Spain, Italy)
Study setting	Hospital setting
Study dates	RECUR database data from January 2006 to December 2011
Sources of funding	None declared
Inclusion criteria	Adults (18 years or over) who have been treated for localised or locally advanced RCC
Exclusion criteria	Adults with metastatic disease
Intervention(s)	1) Cross-sectional (computed tomography, magnetic resonance imaging) and conventional chest x-ray, ultrasound without following specific guidelines. 2) higher imaging frequency: post hoc classification of individuals by whether their imaging frequency was higher or lower than the median. Intervention is higher than median. For both, time points for follow-up imaging were based on the follow-up protocols of the respective treating centres and their local standards.

Comparator	1) Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50% versus <50% 2) higher imaging frequency: post hoc classification of individuals by whether their imaging frequency was higher or lower than the median. Comparator is lower than median. For both, short-term follow-up (0-2.49 years) versus mid-term follow-up (2.5-5.49 years) versus long-term follow-up (>5.5 years)
Outcome measures	Overall survival Recurrence
Number of participants	N=1,612
Duration of follow-up	Median (interquartile range): 63 (58–76) months
Loss to follow-up	Overall, 1,889 patients were included in RECUR. 164 were excluded from the analysis due to lack of baseline data or death <90 days after primary surgery. Furthermore, 111 patients were excluded due to follow-up <4 years and finally, 53 were excluded due to lack of follow-up imaging data.
Methods of analysis	No additional information
Additional comments	Patients were stratified into low-, intermediate-, and high-risk groups according to the Leibovich score in cases of predominantly clear cell RCC, and the University of California Los Angeles Integrated Staging System (UISS) system for non–clear cell RCC subtypes. In total 4,929 imaging procedures (28%) were CT abdomen, 3,024 (17%) were CT thorax, 6,540 (38%) were chest x-ray, 2,651 (15%) were ultrasound and 189 (1.1%) were abdominal MRIs. In total, 6540 imaging procedures (38%) were conventional chest x-ray and 2651 (15%) were ultrasound. **Narrative results:** No significant difference in overall survival between potentially curable and probably incurable* patients stratified for the type of imaging resulting in detection of their recurrence. No significant difference in overall survival after recurrence based on high (≥50%) or low (<50%) cross-sectional imaging percentage during follow-up. * Potentially curable was taken to be local recurrence, single metastasis or oligometastatic (≤ 3 lesions at a single site). All other recurrence was considered probably incurable.

Study arms

Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50% (N = NR)

Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) <50% (N = NR)

Characteristics

Study-level characteristics

Characteristic	Study (N = 1612)
% Female Sample size	n = 576 ; % = 35.7
Mean age (SD) (years) Age at surgery Mean (SD)	62.9 (NR)
Median age (IQR) - at recruitment (years) Median (IQR)	64 (55 to 72)
Condition status - low risk Sample size	n = 806 ; % = 50
Condition status - intermediate risk Sample size	n = 497 ; % = 30.8
Condition status - High risk Sample size	n = 309 ; % = 19.2
Comorbidities Nominal	NR

Outcomes

Non-symptomatic recurrence – ≥50% cross-sectional imaging vs. <50% cross-sectional imaging

Non-symptomatic recurrence out of total recurrence detection

Outcome	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50%, , N = 35	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) <50%, , N = 30	Low imaging frequency, , N = 32	High imaging frequency, , N = 33
Non-symptomatic recurrence out of total recurrence detected - low risk No of events	n = 25 ; % = 71.43	n = 15 ; % = 50	n = 17 ; % = 53.1	n = 23 ; % = 69.7

Non-symptomatic recurrence out of total recurrence detected - low risk - Polarity - Higher values are better

Non-symptomatic recurrence out of total recurrence detection

Outcome	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50%, , N = 56	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) <50%, , N = 52	Low imaging frequency,, N = 53	High imaging frequency, , N = 39
Non symptomatic recurrence out of total recurrence detected - intermediate risk No of events	n = 40 ; % = 71.43	n = 32 ; % = 61.54	n = 32 ; % = 60.4	n = 30 ; % = 76.9

Non symptomatic recurrence out of total recurrence detected - intermediate risk - Polarity - Higher values are better

Non-symptomatic recurrence out of total recurrence detection

Outcome	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50%, , N = 119	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) <50%, , N = 44	Low imaging frequency, , N = 75	High imaging frequency, , N = 84
Non symptomatic recurrence out of total recurrence detected - high risk No of events	n = 69 ; % = 57.98	n = 30 ; % = 68.18	n = 45 ; % = 60	n = 54 ; % = 64.3

Non symptomatic recurrence out of total recurrence detected - high risk - Polarity - Higher values are better

Non-symptomatic recurrence out of total recurrence detection

Outcome	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50%, , N = 210	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) <50%, , N = 126	Low imaging frequency, , N = 160	High imaging frequency, , N = 156
Non symptomatic recurrence out of total recurrence detected - overall risk No of events	n = 134 ; % = 63.81	n = 77 ; % = 61.11	n = 94 ; % = 58.8	n = 107 ; % = 68.6

Non symptomatic recurrence out of total recurrence detected - overall risk - Polarity - Higher values are better

Recurrence detected in regular follow-up

Outcome	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50%, , N = 35	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) <50%, , N = 30	Low imaging frequency, , N = 32	High imaging frequency, , N = 33
Recurrence detected in regular follow-up out of total recurrence - low risk No of events	n = 24 ; % = 68.57	n = 15 ; % = 50	n = 17 ; % = 53.1	n = 22 ; % = 66.7

Recurrence detected in regular follow-up

Outcome	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50%, , N = 56	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) <50%, , N = 52	Low imaging frequency, , N = 53	High imaging frequency, , N = 47
Recurrence detected in regular follow-up out of total recurrence - intermediate risk No of events	n = 48 ; % = 85.71	n = 30 ; % = 57.69	n = 34 ; % = 64.2	n = 39 ; % = 83

Recurrence detected in regular follow-up

Outcome	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50%, , N = 119	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) <50%, , N = 44	Low imaging frequency, , N = 80	High imaging frequency, , N = 35
Recurrence detected in regular follow-	n = 90 ; % = 75.63	n = 31 ; % = 70.45	n = 53 ; % = 66.3	n = 27 ; % = 77.1

Outcome	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50%, , N = 119	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) <50%, , N = 44	Low imaging frequency, , N = 80	High imaging frequency, , N = 35
up out of total recurrence - high risk No of events				

Recurrence detected in regular follow-up

Outcome	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) ≥50%, , N = 210	Cross sectional imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) <50%, , N = 126	Low imaging frequency, , N = 165	High imaging frequency, , N = 115
Recurrence detected in regular follow-up out of total recurrence - overall risk No of events	n = 162 ; % = 77.14	n = 76 ; % = 60.32	n = 104 ; % = 63	n = 88 ; % = 76.5

Critical appraisal ROBINS-I: a tool for non-randomised studies of interventions

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(Confounding due to the impact of varying frequencies of imaging; the methods of imaging within CSI and conventional imaging groups also varied, and it was not clear how many patients within each of the groups received each type of imaging. Participants with incomplete follow-up datasets and <4 years follow-up were excluded from the final cohort. Frequency of imaging per year were only reported as median (IQR) values.)*
Overall bias	Directness	Directly applicable

Dabestani, 2019b

Bibliographic Reference	Dabestani, Saeed; Beisland, Christian; Stewart, Grant D; Bensalah, Karim; Gudmundsson, Eirikur; Lam, Thomas B; Gietzmann, William; Zakikhani, Paimaun; Marconi, Lorenzo; Fernandez-Pello, Sergio; Monagas, Serenella; Williams, Samuel Paul; Torbrand, Christian; Powles, Thomas; Van Werkhoven, Erik; Meijer, Richard; Volpe, Alessandro; Staehler, Michael; Ljungberg, Borje; Bex, Axel; Intensive Imaging-based Follow-up of Surgically Treated Localised Renal Cell Carcinoma Does Not Improve Post-recurrence Survival: Results from a European Multicentre Database (RECUR).; European urology; 2019; vol. 75 (no. 2); 261-264

Study details

Other publications associated with this study included in review	Dabestani et al. Increased use of cross-sectional imaging for follow-up does not improve post-recurrence survival of surgically treated initially localized R.C.C.: results from a European multicenter database (R.E.C.U.R.). Scandinavian journal of urology; 2019; vol. 53 (no. 1); 14-20.
Study type	Retrospective cohort study
Study location	Eight European countries (Sweden, Iceland, United Kingdom, Norway, The Netherlands, Portugal, Spain, Italy)
Study setting	Hospital setting
Study dates	RECUR database data from January 2006 - December 2011
Sources of funding	None declared.
Inclusion criteria	Adults (18 years or over) who have been treated for localised or locally advanced RCC
Exclusion criteria	Adults with metastatic disease
Intervention(s)	Cross-sectional (computed tomography, magnetic resonance imaging) and conventional chest x-ray, ultrasound without following specific guidelines. Time points for follow-up imaging were based on the follow-up protocols of the respective treating centres and their local standards.
Comparator	European association of Urology (EAU) guideline for follow-up.
Outcome measures	Overall survival (narrative results only)
Number of participants	N=1,612
Duration of follow-up	Median (interquartile range): 63 (58–76) months

Loss to follow-up	Overall, 1,889 patients were included in RECUR. 164 were excluded from the analysis due to lack of baseline data or death <90 days after primary surgery. Furthermore, 111 patients were excluded due to follow-up <4 years and finally, 53 were excluded due to lack of follow-up imaging data.
Methods of analysis	No additional information
Additional comments	Patients were stratified into low-, intermediate-, and high-risk groups according to the Leibovich score in cases of predominantly clear cell RCC, and the University of California Los Angeles Integrated Staging System (U.I.S.S.) system for non–clear cell RCC subtypes. The total number of imaging procedures per patient were compared to the suggested 2017 EAU guideline for follow-up for a patient in the corresponding risk group. Imaging ratio defined as the total number of imaging scans divided by recommended number of imaging scans (from the EAU 2017 guideline). **Narrative results:** No significant differences in overall survival after recurrence for patients with imaging ratio of ≤0.75, 0.76-1.99 and ≥2.0.

Study arms

Cross sectional imaging (computed tomography and magnetic resonance imaging) and conventional imaging (chest x ray and ultrasound) (N = NR)

Imaging without following specific guideline for follow-up

EAU guideline for follow-up (N = NR)

The 2017 European Association of Urology guidelines for follow-up recommendations were used as a comparator

Characteristics

Study-level characteristics

Characteristic	Study (N = 1612)
% Female No of events	n = 580 ; % = 36
Mean age (SD) Age at surgery Mean (SD)	62.9 (0.3)

Characteristic	Study (N = 1612)
Condition status - Low risk No of events	n = 806 ; % = 50
Condition status - Intermediate risk No of events	n = 500 ; % = 31
Condition status - High risk No of events	n = 306 ; % = 19
Comorbidities Nominal	NR

Critical appraisal- ROBINS-I: a tool for non-randomised studies of interventions

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(Confounding due to various different follow-up strategies were used without details given. Some patients were excluded following the start of follow-up because of follow-up<4 years and lack of follow-up imaging data. Different imaging modalities received so outcomes could be dependent on sensitivity of each of the imaging modalities.)*
Overall bias	Directness	Directly applicable

Gires, 2019

Bibliographic Reference	Gires, Baptiste; Khene, Zine-Eddine; Bigot, Pierre; Alimi, Quentin; Peyronnet, Benoit; Verhoest, Gregory; Manunta, Andrea; Bensalah, Karim; Mathieu, Romain; Impact of routine imaging in the diagnosis of recurrence for patients with localized and locally advanced renal tumor treated with nephrectomy.; World journal of urology; 2019; vol. 37 (no. 12); 2727-2736

Study details

Other publications associated with this study	None - no additional information.

included in review	
Study type	Retrospective cohort study
Study location	France
Study setting	Hospital - single centre
Study dates	The charts of patients from 2006 to 2010 in an academic department of urology were retrospectively reviewed.
Sources of funding	Not reported - no additional information.
Inclusion criteria	Adults (18 years or over) who have been treated for localised or locally advanced RCC
Exclusion criteria	Adults with metastatic disease
Intervention(s)	"Inadequate" follow-up was defined as anything which did not correspond precisely to the recommendations of the UCLA UISS protocol. Follow-up modalities were determined according to the surgeon's discretion. The type of imaging (chest X-ray, chest computerized tomography (CT) scan, abdominal ultrasound, abdominal CT scan or magnetic resonance imaging (MRI)) was also recorded.
Comparator	"Adequate" follow-up was defined as anything which corresponded precisely to the recommendations of the UCLA UISS protocol.
Outcome measures	Overall survival Recurrence Cancer specific survival Recurrence free survival
Number of participants	N= 267
Duration of follow-up	Median (IQR): 72 (51-92) months.
Loss to follow-up	Retrospective study; no loss to follow-up. No additional information.
Methods of analysis	Recurrence-free survival, cancer specific survival and overall survival were estimated using the Kaplan–Meier method and compared between groups with the log-rank test.
Additional comments	The study reported no significant difference between the adequate follow-up group and the inadequate follow-up group for recurrence free survival

	(log rank, p=0.93), cancer-specific survival (p=0.46) and overall survival (p=0.91).

Study arms

Adequate follow-up (N = 146)

"Adequate" follow-up was defined as anything which corresponded precisely to the recommendations of the UCLA UISS protocol.

Inadequate follow-up (N = 121)

"Inadequate" follow-up Imaging examinations more spaced out/delayed than what is recommended in the UCLA UISS protocol.

Characteristics

Study-level characteristics

Characteristic	Study (N = 267)
% Female No of events	n = 98 ; % = 36
Mean age (SD) (years) Age at diagnosis Median (IQR)	60 (50 to 71)
Condition status - Leibovich score 1 No of events	n = 130 ; % = 48.7
Condition status - Leibovich score 2 No of events	n = 78 ; % = 29.2
Condition status - Leibovich score 3 No of events	n = 58 ; % = 21.7
Condition status - Leibovich score - unknown No of events	n = 1
Condition status - UISS score - low risk No of events	n = 105 ; % = 39.3

Characteristic	Study (N = 267)
Condition status - UISS score - intermediate risk No of events	n = 140 ; % = 52.5
Condition status - UISS score - high risk No of events	n = 22 ; % = 8.2
Comorbidities Nominal	NR
ECOG score - 0 No of events	n = 191 ; % = 71.5
ECOG score - 1 No of events	n = 37 ; % = 13.9
ECOG score - 2 No of events	n = 1 ; % = 0.4

Study timepoints

- 72 months (Median value)

Survival outcomes

Outcome	Inadequate follow-up vs Adequate follow-up, 72-month, N = 62
Cancer specific mortality In multivariable analysis, the presence of multi-metastatic lesions at recurrence diagnosis was the only independent prognostic factor of worse CSM (HR = 10.15 (95% CI 2.29 to 44.82, p=0.002) Hazard ratio/95% CI	1.13 (0.53 to 2.42)

Critical appraisal - ROBINS-I: a tool for non-randomised studies of interventions

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Moderate risk of bias for bias due to confounding due to inappropriate analysis of confounding variables)*
Overall bias	Directness	Directly applicable

Appendix E – Forest plots

≥50% cross-sectional imaging vs. <50% cross-sectional imaging

Figure 5: Non-symptomatic recurrence detection out of total recurrence

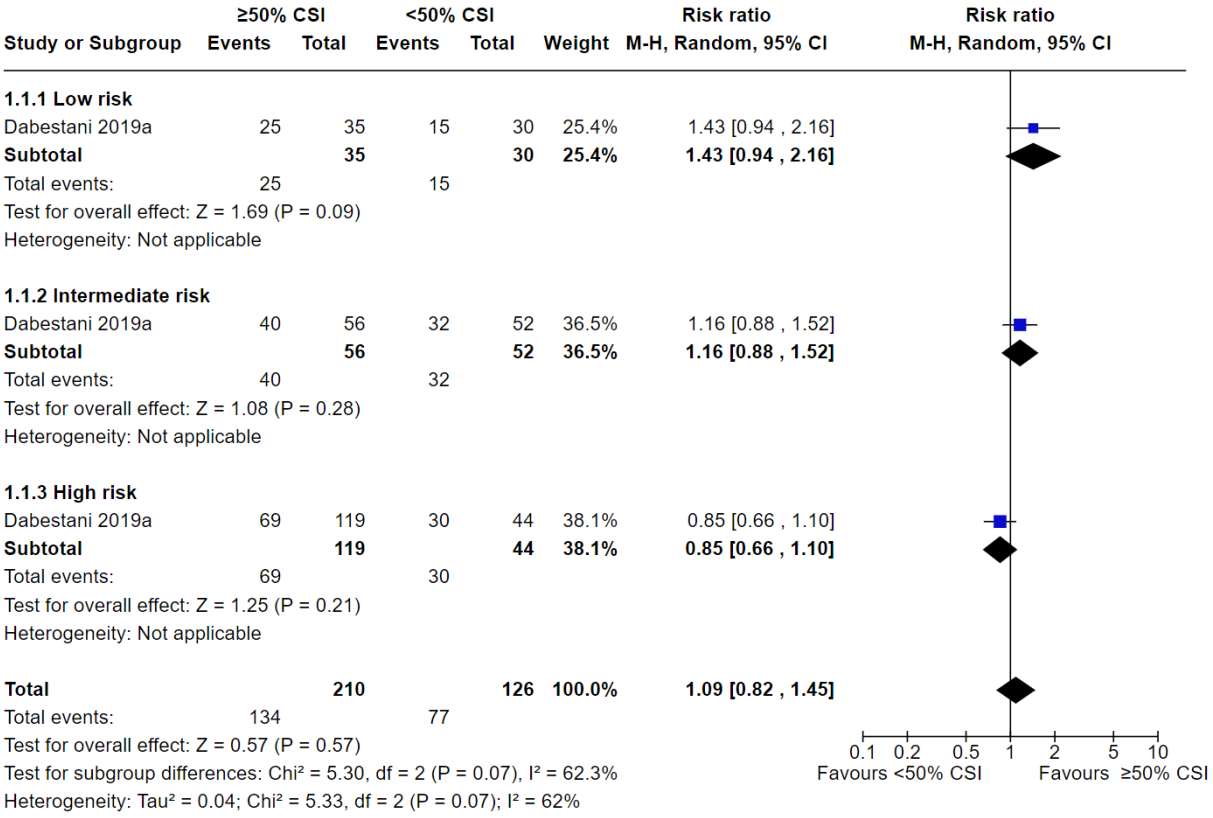
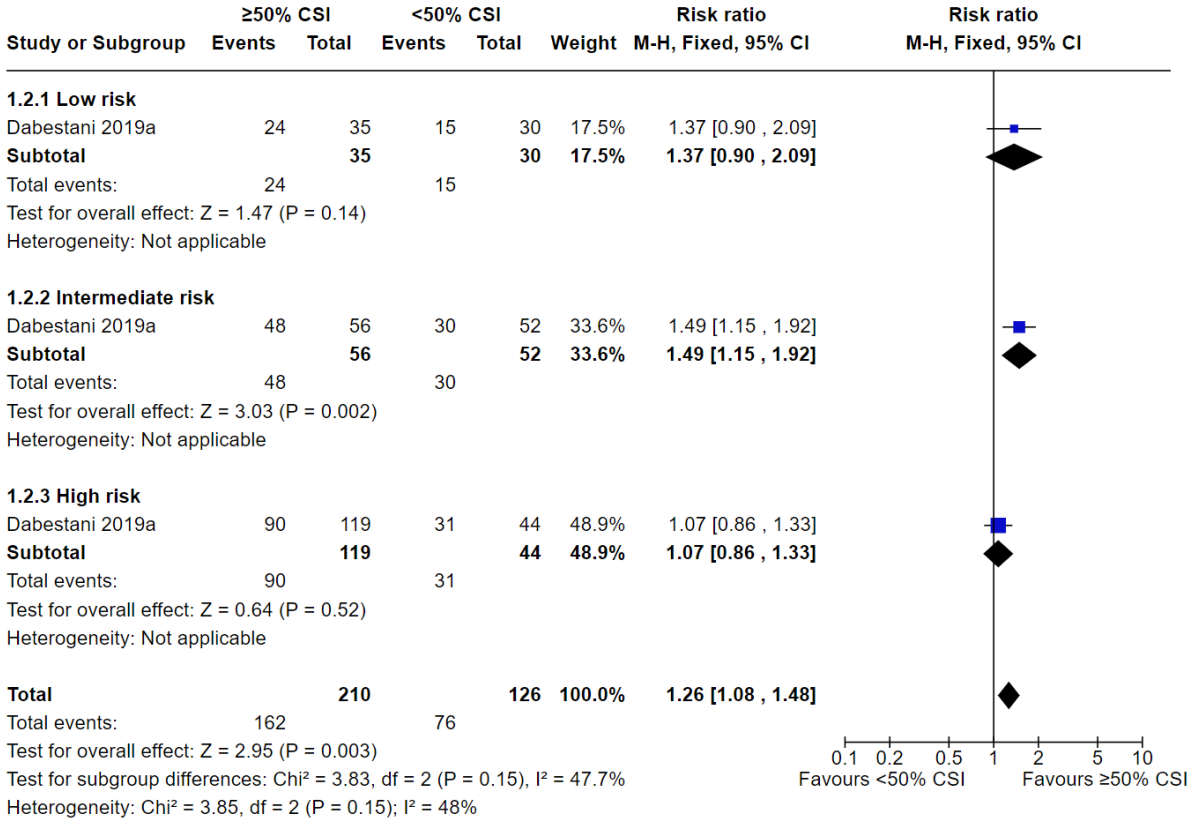


Figure 6: Recurrence detected in regular follow-up out of total recurrence



High (above median) imaging frequency versus low (below median) imaging frequency

Figure 7: Non-symptomatic recurrence detection out of total recurrence

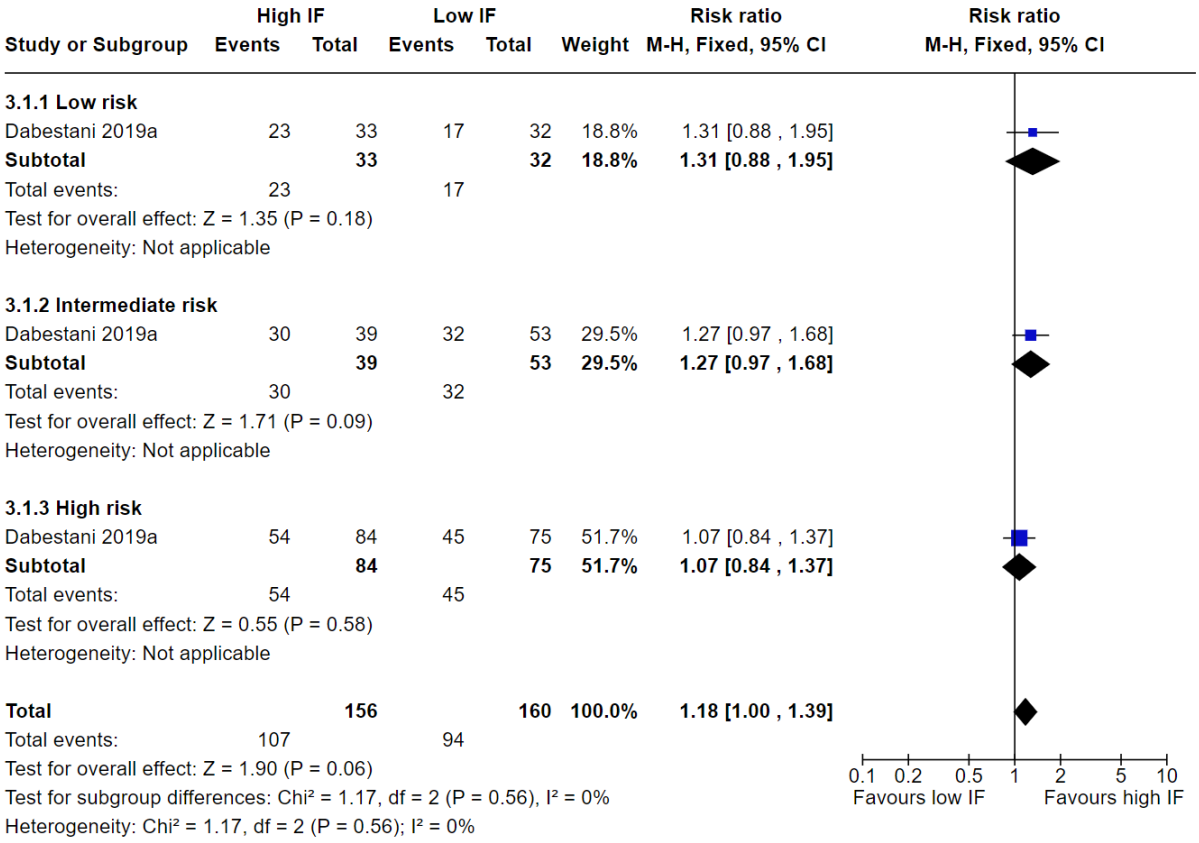
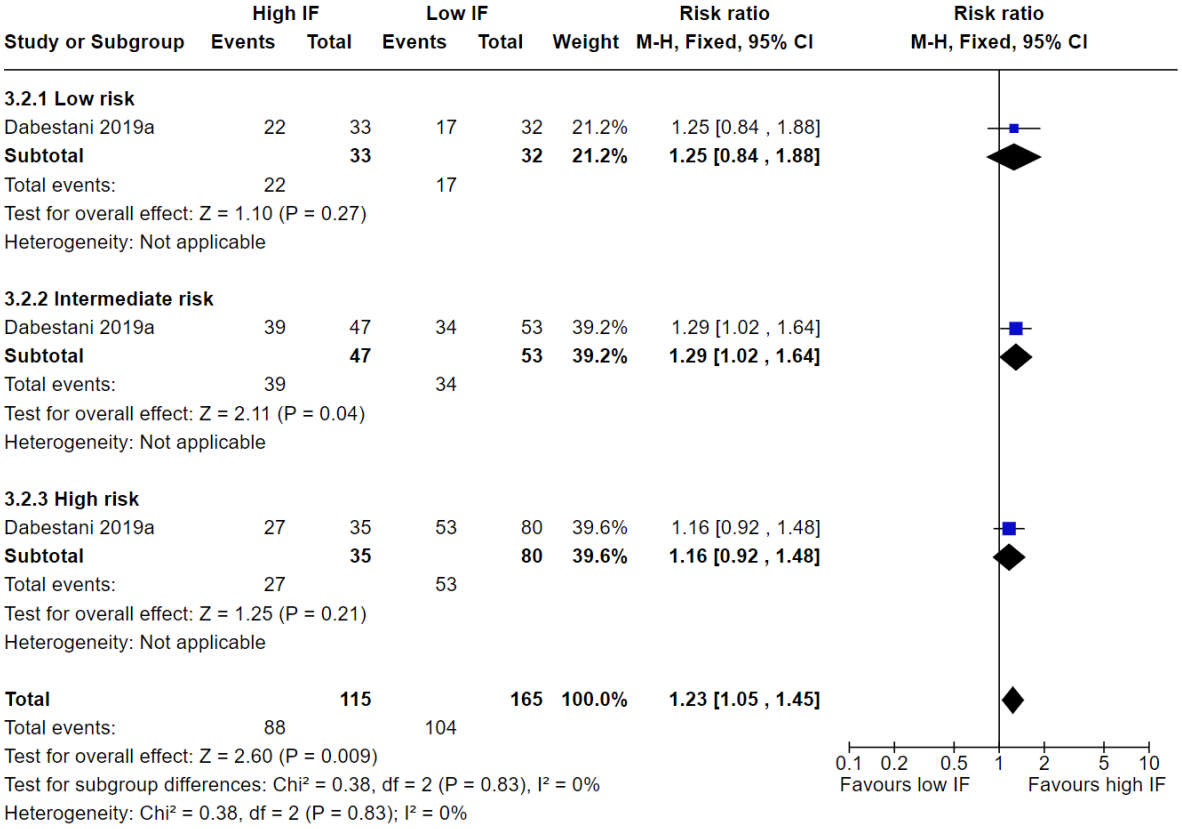
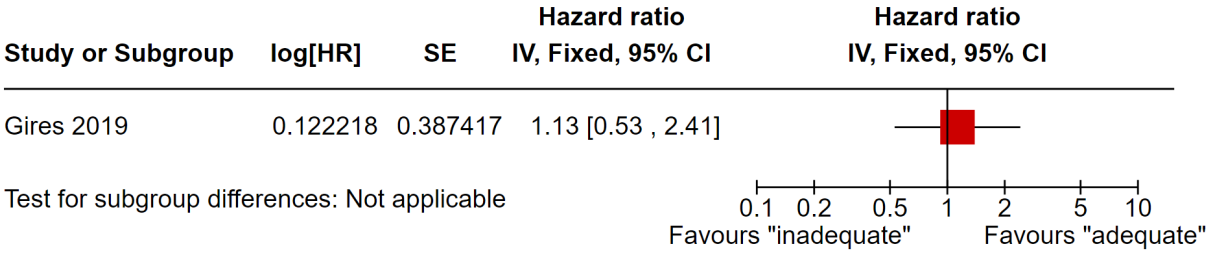


Figure 8: Recurrence detected in regular follow-up out of total recurrence



"Inadequate" follow-up (imaging <UISS recommendations) vs. "adequate" follow-up (UISS surveillance protocol)

Figure 9: Cancer-specific survival after recurrence



Appendix F – GRADE tables

Table 9: ≥ 50% Cross-Sectional Imaging (CSI) compared to < 50% Cross-Sectional Imaging (CSI)

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**≥ 50% Cross-Sectional Imaging (CSI)**	**< 50% Cross-Sectional Imaging (CSI) in follow-up imaging**	**Relative (95% CI)**	**Absolute (95% CI)**	
Non-symptomatic recurrence detection (out of total recurrence) - all risk group											
1 (Dabestani 2019a) (n=336)	non-randomised studies	very serious[a]	serious[b]	serious[c]	very serious[e]	none	134/210 (63.8%)	77/126 (61.1%)	**RR 1.09** (0.82 to 1.45)	**55 more per 1,000** (from 110 fewer to 275 more)	Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**≥ 50% Cross-Sectional Imaging (CSI)**	**< 50% Cross-Sectional Imaging (CSI) in follow-up imaging**	**Relative (95% CI)**	**Absolute (95% CI)**	
Recurrence detected in regular follow-up (out of total recurrence) - all risk group											
1 (Dabestani 2019a) (n=336)	non-randomised studies	very serious[a]	serious[b]	serious[c]	serious[d]	none	162/210 (77.1%)	76/126 (60.3%)	**RR 1.26** (1.08 to 1.48)	**163 more per 1,000** (from 54 more to 290 more)	Very low

CI: confidence interval; RR: risk ratio

a. Downgraded twice for risk of bias. >50% of the weight from studies at high risk of bias for this outcome

b. Downgraded once for inconsistency. Analysis included a single study

c. Downgraded once for indirectness. Intervention indirectness - the follow-up received was not based on a pre-specified protocol to which people were allocated based on risk. The different "follow-up groups" each contained a mix of low-, medium- and high-risk individuals.

d. Downgraded once for imprecision. Less than 420 participants contributing to the outcome

Table 10: High (above median) imaging frequency versus low (below median) imaging frequency

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High imaging frequency**	**Low imaging frequency**	**Relative (95% CI)**	**Absolute (95% CI)**	
Non-symptomatic recurrence detection (out of total recurrence) - all risk group											
1 (Dabestani 2019a) (n=316)	non-randomised studies	very serious[a]	serious[b]	serious[c]	very serious[d]	none	107/156 (68.6%)	94/160 (58.8%)	**RR 1.18** (1.00 to 1.39)	**106 more per 1,000** (from 0 fewer to 229 more)	Very low
Recurrence detected in regular follow-up (out of total recurrence) - all risk group											
1 (Dabestani 2019a) (n=280)	non-randomised studies	very serious[a]	serious[b]	serious[c]	serious[e]	none	88/115 (76.5%)	104/165 (63.0%)	**RR 1.23** (1.04 to 1.45)	**145 more per 1,000** (from 32 more to 284 more)	Very low

CI: confidence interval; RR: risk ratio

a. Downgraded twice for risk of bias. >50% of the weight from studies at high risk of bias for this outcome

b. Downgraded once for inconsistency. Analysis included a single study

c. Downgraded once for indirectness. Intervention indirectness - the follow-up received was not based on a pre-specified protocol to which people were allocated based on risk. The different "follow-up groups" each contained a mix of low-, medium- and high-risk individuals.
d. Downgraded twice for imprecision. 95% confidence interval includes the line of no effect and less than 420 participants contributing to the outcome
e. Downgraded once for imprecision. Fewer than 420 participants contributing to the outcome

Table 11: Inadequate follow-up (follow-up imaging examinations more spaced out/delayed than what is recommended in the UCLA UISS surveillance protocol) compared to adequate follow-up (defined as anything which corresponded precisely to the recommendations of the UCLA UISS surveillance protocol) for people who have been treated for localised or locally advanced RCC

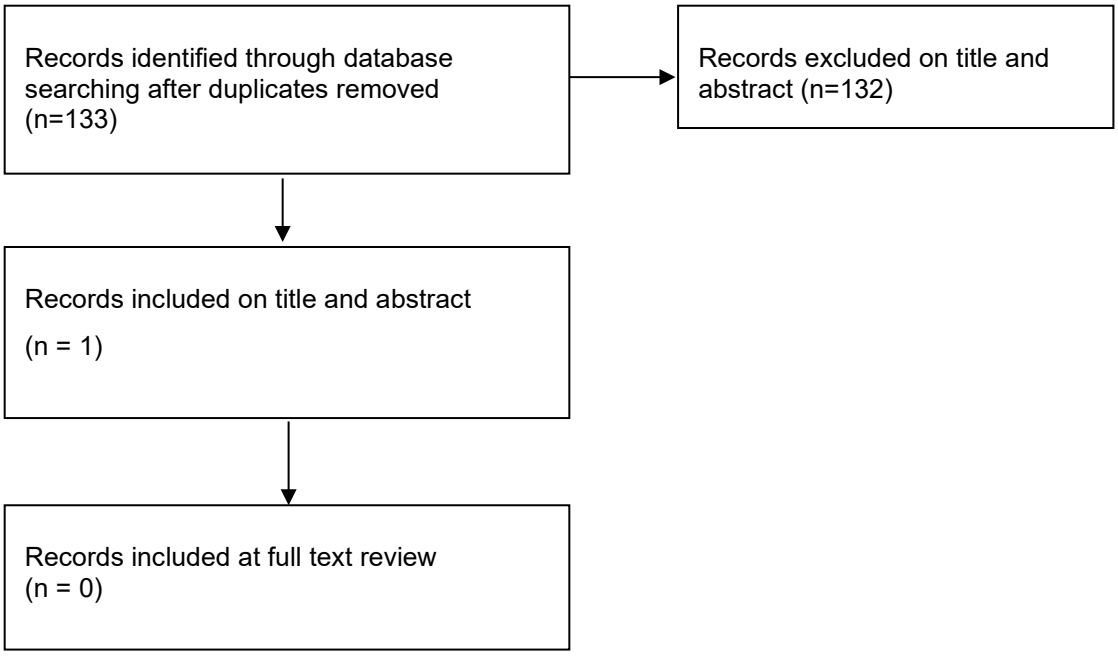
Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**inadequate follow-up (follow-up Imaging examinations more spaced out/delayed than what is recommended in the UCLA UISS surveillance protocol)**	**adequate follow-up (defined as anything which corresponded precisely to the recommendations of the UCLA UISS surveillance protocol)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Cancer specific survival after recurrence											
1 (Gires 2019)	non-randomised studies	serious[a]	serious[b]	serious[c]	very serious[d]	none	NR	NR	**HR 1.13** (0.53 to 2.42)	**not estimable**	Very low

CI: confidence interval; HR: hazard ratio
a. Downgraded once for risk of bias. >50% of the weight of the outcome came from a study with some concerns in risk of bias
b. Downgraded once for inconsistency. Analysis included a single study

c. Downgraded once for indirectness. The evidence was downgraded due to an indirect comparison. The study compared a risk stratified follow-up protocol with less follow-up than what was recommended by that protocol.
d. Downgraded twice for imprecision. 95% CI crosses the line of no effect and fewer than 420 participants contributing to this outcome

Appendix G – Economic evidence study selection

Figure 10: Economic evidence study selection



Appendix H – Economic evidence tables

No evidence was identified which was applicable to this review question.

Appendix I – Health economic model

This review question was prioritised for original economic modelling. Details of the economic analysis are described in the accompanying economic report.

Appendix J – Excluded studies

Effectiveness excluded studies (N=34)

Table 12: Excluded effectiveness studies

Study	Reason
Antonelli, Alessandro, Cozzoli, Alberto, Zani, Danilo et al. (2007) The follow-up management of non-metastatic renal cell carcinoma: definition of a surveillance protocol. BJU international 99(2): 296-300	- Not a relevant study design: non-comparative study
Azawi, Nessn H, Tesfalem, Helen, Mosholt, Karina Sif Sondergaard et al. (2016) Recurrence rates and survival in a Danish cohort with renal cell carcinoma. Danish medical journal 63(4)	- Not a relevant study design: non-comparative study
Beisland, Christian, Gubrandsdottir, Gigja, Reisaeter, Lars A R et al. (2016) A prospective risk-stratified follow-up programme for radically treated renal cell carcinoma patients: evaluation after eight years of clinical use. World journal of urology 34(8): 1087-99	- Not a relevant study design: non-comparative study
Bimbatti, Davide, Ciccarese, Chiara, Fantinel, Emanuela et al. (2018) Predictive role of changes in the tumor burden and International Metastatic Renal Cell Carcinoma Database Consortium class during active surveillance for metastatic renal cell carcinoma. Urologic oncology 36(12): 526e13-526e18	- Not a relevant study design: non-comparative study
Capogrosso, Paolo, Capitanio, Umberto, La Croce, Giovanni et al. (2016) Follow-up After Treatment for Renal Cell Carcinoma: The Evidence Beyond the Guidelines. European urology focus 1(3): 272-281	- Systematic review used as source of primary studies
Correa, Andres F, Jegede, Opeyemi A, Haas, Naomi B et al. (2021) Predicting Disease Recurrence, Early Progression, and Overall Survival Following Surgical Resection for High-risk Localized and Locally Advanced Renal Cell Carcinoma. European urology 80(1): 20-31	- Study does not contain a relevant intervention
Dabestani, Saeed, Beisland, Christian, Stewart, Grant D et al. (2019) Long-term Outcomes of Follow-up for Initially Localised	- Study does not contain a relevant intervention

Study	Reason
Clear Cell Renal Cell Carcinoma: RECUR Database Analysis. European urology focus 5(5): 857-866	*Study did not assess approaches to follow-up, instead studied the outcomes following treatment after a period of follow-up*
Dabestani, Saeed, Marconi, Lorenzo, Kuusk, Teele et al. (2018) Follow-up after curative treatment of localised renal cell carcinoma. World journal of urology 36(12): 1953-1959	- Review article but not a systematic review
Dion, Marie, Martinez, Carlos H, Williams, Andrew K et al. (2010) Cost analysis of two follow-up strategies for localized kidney cancer: a Canadian cohort comparison. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 4(5): 322-6	- Population not risk stratified
Eggener, Scott E, Yossepowitch, Ofer, Pettus, Joseph A et al. (2006) Renal cell carcinoma recurrence after nephrectomy for localized disease: predicting survival from time of recurrence. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 24(19): 3101-6	- Not a relevant study design: non-comparative study
Eiken, P.W., Atwell, T.D., Kurup, A.N. et al. (2018) Imaging following renal ablation: what can we learn from recurrent tumors?. Abdominal Radiology 43(10): 2750-2755	- Study does not contain a relevant intervention - Does not contain relevant outcomes
Ged, Yasser, Chen, Ying-Bei, Knezevic, Andrea et al. (2019) Metastatic Chromophobe Renal Cell Carcinoma: Presence or Absence of Sarcomatoid Differentiation Determines Clinical Course and Treatment Outcomes. Clinical genitourinary cancer 17(3): e678-e688	- Study does not contain a relevant intervention
Jamil, Marcus L, Keeley, Jacob, Sood, Akshay et al. (2020) Long-term Risk of Recurrence in Surgically Treated Renal Cell Carcinoma: A Post Hoc Analysis of the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network E2805 Trial Cohort. European urology 77(2): 277-281	- Not a relevant study design: non-comparative study
Juul, Simon, Donskov, Frede, Clark, Peter E et al. (2022) GRade, Age, Nodes, and Tumor (GRANT) compared with Leibovich score to predict survival in localized renal cell carcinoma: A nationwide study.	- Study does not contain a relevant intervention

Study	Reason
International journal of urology : official journal of the Japanese Urological Association 29(7): 641-645	
Kuijpers, Y A M, Meijer, R P, Jonges, G N et al. (2016) Potentially curable recurrent disease after surgically managed non-metastatic renal cell carcinoma in low-, intermediate- and high-risk patients. World journal of urology 34(8): 1073-9	- Not a relevant study design: non-comparative study
Laguna, M Pilar (2019) Re: Intensive Imaging-Based Follow-up of Surgically Treated Localised Renal Cell Carcinoma Does Not Improve Post-Recurrence Survival: Results from a European Multicentre Database (RECUR). The Journal of urology 202(3): 455-456	- Conference abstract
Lam, John S, Leppert, John T, Figlin, Robert A et al. (2005) Surveillance following radical or partial nephrectomy for renal cell carcinoma. Current urology reports 6(1): 7-18	- Review article but not a systematic review
Laouris, Panayiotis, Re, Chiara, Stimpson, Georgia et al. (2025) Feasibility study of using the PREDICT kidney tool for patients with localised renal cell carcinoma. BJUI compass 6(4): e70014	- Not a relevant study design *Protocol only*
Margue, Gaelle, Ferrer, Loic, Etchepare, Guillaume et al. (2024) UroPredict: Machine learning model on real-world data for prediction of kidney cancer recurrence (UroCCR-120). NPJ precision oncology 8(1): 45	- Study does not contain a relevant intervention
Martini, Alberto, Bernhard, Jean-Christophe, Falagario, Ugo G et al. (2024) Oncologic surveillance after surgical treatment for clinically localized kidney cancer: UroCCR study n. 129. Minerva urology and nephrology 76(5): 578-587	- Not a relevant study design: non-comparative study
McIntosh, A.G., Ristau, B.T., Ruth, K. et al. (2019) Re: Active surveillance for localized renal masses: Tumor growth, delayed intervention rates, and >5-yr clinical outcomes. Journal of Urology 201(3): 440	- Not a relevant study design *Editorial comment*
McIntosh, Andrew G, Ristau, Benjamin T, Ruth, Karen et al. (2018) Active	- Does not contain a relevant population of people

Study	Reason
Surveillance for Localized Renal Masses: Tumor Growth, Delayed Intervention Rates, and >5-yr Clinical Outcomes. European urology 74(2): 157-164	*Population has not undergone any treatment. Population includes people with masses or enhancing cysts undergoing active surveillance*
Meng, Max (2017) Laparoscopic cryoablation for renal cell carcinoma: 100-Month oncologic outcomes. Caputo PA, Ramirez D, Zargar H, Akca O, Andrade HS, O'Malley C, Remer EM, Kaouk JH. J Urol. 2015 Oct;194(4):892-896. [Epub 2015 April 23]. doi: 10.1016/j.juro.2015.03.128. Urologic oncology 35(5): 311-312	- Conference abstract
Popert, R J; Vinnicombe, J; Coptcoat, M J (1993) Ultrasound in renal carcinoma: an essential in follow-up. British journal of urology 72(2): 148-52	- Not a relevant study design: non-comparative study
Purysko, Andrei S, Nikolaidis, Paul, Khatri, Gaurav et al. (2022) ACR Appropriateness Criteria R Post-Treatment Follow-up and Active Surveillance of Clinically Localized Renal Cell Carcinoma: 2021 Update. Journal of the American College of Radiology : JACR 19(5s): 156-s174	- Review article but not a systematic review - Not a relevant study design *Not an intervention study. Study is a literature review*
Santoni, Matteo, Buti, Sebastiano, Myint, Zin W et al. (2024) Real-world Outcome of Patients with Advanced Renal Cell Carcinoma and Intermediate- or Poor-risk International Metastatic Renal Cell Carcinoma Database Consortium Criteria Treated by Immune-oncology Combinations: Differential Effectiveness by Risk Group?. European urology oncology 7(1): 102-111	- Study does not contain a relevant intervention
Sanz, Enrique, Hevia, Vital, Arias, Fernando et al. (2015) Contrast-enhanced ultrasound (CEUS): an excellent tool in the follow-up of small renal masses treated with cryoablation. Current urology reports 16(1): 469	- Does not contain relevant outcomes - Study does not contain a relevant intervention
Siva, Shankar, Louie, Alexander V, Kotecha, Rupesh et al. (2024) Stereotactic body radiotherapy for primary renal cell carcinoma: a systematic review and practice guideline from the International Society of Stereotactic Radiosurgery (ISRS). The Lancet. Oncology 25(1): e18-e28	- Study does not contain a relevant intervention

Study	Reason
Skolarikos, Andreas, Alivizatos, Gerasimos, Laguna, Pilar et al. (2007) A review on follow-up strategies for renal cell carcinoma after nephrectomy. European urology 51(6): 1490-1501	- Review article but not a systematic review
Stewart-Merrill SB, Thompson RH, Boorjian SA et al. (2015) Oncologic Surveillance After Surgical Resection for Renal Cell Carcinoma: A Novel Risk-Based Approach. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33(35): 4151-4157	- Not a relevant study design: non-comparative study
Usher-Smith, Juliet A, Li, Lanxin, Roberts, Lydia et al. (2022) Risk models for recurrence and survival after kidney cancer: a systematic review. BJU international 130(5): 562-579	- Systematic review used as source of primary studies
van Oostenbrugge, Tim J, Kroeze, Stephanie G C, Bosch, J L H Ruud et al. (2015) The blind spots in follow-up after nephrectomy or nephron-sparing surgery for localized renal cell carcinoma. World journal of urology 33(6): 881-7	- Not a relevant study design: non-comparative study
Williamson, Timothy J, Pearson, John R, Ischia, Joseph et al. (2016) Guideline of guidelines: follow-up after nephrectomy for renal cell carcinoma. BJU international 117(4): 555-62	- Not a relevant study design: non-comparative study
Yang, Guangjie, Nie, Pei, Yan, Lei et al. (2022) The radiomics-based tumor heterogeneity adds incremental value to the existing prognostic models for predicting outcome in localized clear cell renal cell carcinoma: a multicenter study. European journal of nuclear medicine and molecular imaging 49(8): 2949-2959	- Non-OECD country

HE excluded studies

Economic excluded studies N=1

Table 13: Excluded economic studies

Study	Reason
Tyson, Mark D and Chang, Sam S (2017) Optimal Surveillance Strategies After Surgery for Renal Cell Carcinoma. Journal of the National Comprehensive Cancer Network: JNCCN 15(6): 835-840	- Did not compare costs - US cost perspective

Appendix K– Research recommendations

K1.1 Research recommendation

For people who have had treatment for localised or locally advanced renal cell carcinoma, what are the most clinically and cost-effective risk of recurrence stratified follow-up strategies (based on method, duration and frequency)?

K1.1.1 Why this is important

People who have been treated for localised or locally advanced renal cell carcinoma with curative intent are moved out of active treatment to receive follow-up which consists of regular imaging and other tests such as blood and urine testing. It is necessary to balance the harms of excess radiation exposure, financial implications for the NHS and the impact on people in terms of anxiety, time and energy with the benefits of accurately identifying recurrence – not only for survival purposes but also for the potential of improving a person's quality of life by identifying a potentially painful and symptomatic recurrence sooner.

K1.1.2 Rationale for research recommendation

Table 14: Rationale for research recommendation

Importance to 'patients' or the population	An evidence-based follow-up protocol for people who have been treated for localised or locally advanced renal cell carcinoma (RCC) could limit unnecessary imaging and associated anxiety whilst also detecting recurrence at an appropriate time point.
Relevance to NICE guidance	Follow-up protocols for people who have been treated for localised or locally advanced RCC have been considered in this guideline but there was a lack of evidence identified which directly compared two follow-up strategies.
Relevance to the NHS	Detection of recurrence could have a downstream impact and improve survival outcomes if detection leads to effective treatment. Likewise reducing unnecessary imaging will reduce imaging needs in the NHS. It could help predict imaging needs in the NHS for people who have been treated for localised or locally advanced RCC.
National priorities	Low
Current evidence base	There is a lack of evidence for pre-specified follow-up protocols for people with local or locally advanced RCC compared directly to each other.
Equality considerations	None known

K1.1.3 Modified PICO table

Table 15: Modified PICO table

Population	Adults (over 18 years) who have been treated for localised or locally advanced renal cell carcinoma (RCC).
Intervention	Risk stratified (risk of recurrence or death) follow-up protocols which might include: • frequency of follow-up • Method of follow-up (method may include blood tests, imaging, and/or other monitoring methods) • duration of follow-up
Comparator	Different risk stratified follow-up protocols compared to each other. (The protocols may differ in terms of follow-up duration, frequency and types of imaging/ tests carried out.)
Outcome	• Survival • Recurrence • Quality of Life • Long term consequences of treatment after detection of recurrence e.g. glomerular filtration rate • Cost effectiveness
Study design	Comparative study design; ideally RCTs
Timeframe	Long term
Additional information	Outcomes should be sub grouped by: • Relevant comorbidities • Ethnicity • Sex • RCC subtype