National Institute for Health and Care Excellence

Kidney cancer: diagnosis and management

[I2] Evidence review for additional imaging tests for differentiating types of renal lesions

NICE guideline [number]
Evidence review underpinning recommendations 1.2.5 to 1.2.6 and a research recommendation in the NICE guideline

September 2025

Draft for consultation

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ISBN: xxx

Contents

Diagnosis and assessment of renal cell carcinoma: additional imaging

1.1 Review questions

1. What is the clinical and cost effectiveness of 99mTc-sestamibi SPECT/CT compared with contrast-enhanced ultrasound for differentiating and managing renal lesions in adults with suspected renal cell carcinoma?

2. In adults with suspected renal cell carcinoma, what is the diagnostic accuracy and cost effectiveness of:

   - 99mTc-sestamibi SPECT/CT
   - contrast-enhanced ultrasound

   for differentiating renal lesions?

1.1.1 Introduction

Early diagnosis of renal cell carcinoma (RCC) allows for the best chance of curative treatment, thereby reducing morbidity and mortality. Most instances of RCC are diagnosed incidentally.

Initial imaging of people with suspected RCC involves triple phase contrast-enhanced CT (CECT) and/ or contrast enhanced MRI (CEMRI). However, there may be situations where CECT and CEMRI results are equivocal and additional imaging is needed to determine the type of lesion. In addition, it can be difficult to preoperatively differentiate between certain types of renal lesions using these imaging techniques. Without a more definitive preoperative diagnosis, people with renal lesions that have suspicious features may undergo partial or radical nephrectomy despite some of these lesions being truly benign. This unnecessary surgery can have adverse effects on quality of life for the individual and wastes valuable NHS resources.

Recent advances in imaging have shown contrast-enhanced ultrasound (CEUS) to be like CT, having the ability to differentiate unclear renal lesions with the added advantage of lower cost and absence of radiation. Imaging with ^{99m}Tc-Sestamibi Single Photon Emission Computed Tomography/Computed Tomography (SPECT/CT) also has the potential to improve the differentiation between benign and solid renal lesions.

This review aims to investigate the diagnostic test accuracy of ^{99m}Tc-sestamibi SPECT/CT for detecting malignancy and CEUS scans for differentiating between solid masses and complex cysts in people presenting with suspected renal cell carcinoma who have already had CECT or CEMRI imaging.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria for question 1 on clinical effectiveness

Population	Adults (18 years or over) with suspected RCC on CT/MRI
Index test	^{99m}Tc-sestamibi SPECT/CT for differentiating between benign and malignant renal lesions
Comparator	Contrast-enhanced ultrasonography (CEUS) for differentiating between a solid mass and complex cyst
Outcomes	• Need for biopsy • Overall survival (death and mortality could be extracted as proxy outcomes) • Quality of life
Study type	• Test and treat RCTs and systematic reviews of test and treat RCTs

CT: computed tomography; MRI: magnetic resonance imaging

Table 2: Modified PICOS inclusion criteria for question 2 on diagnostic test accuracy

Population	Adults (18 years or over) with suspected RCC on CT/MRI
Index test	^{99m}Tc-sestamibi SPECT/CT for differentiating between benign and malignant renal lesions Contrast-enhanced ultrasonography (CEUS) for differentiating between a solid mass and complex cyst
Reference standard	Pathological confirmation of RCC from surgery or biopsy
Outcome measures and clinical outcomes	Diagnostic accuracy outcome measures: • Positive and negative likelihood ratios • Sensitivity and specificity
Study type	• Diagnostic accuracy cross-sectional studies and cohort studies • Systematic reviews of diagnostic accuracy cross-sectional studies

CT: computed tomography; MRI: magnetic resonance imaging

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 specific to this review question are described in the review protocol in appendix A, the methods document and below.

1. Where meta-analysis could not be conducted for statistical reasons, sensitivity and specificity forest plots were obtained from Cochrane RevMan (version 8.16.0) and

likelihood ratio forest plots were obtained from MetaDTA based on the R (RStudio version 2024.12.0) glmer package. The range for the point estimates were presented in the results table as 95% confidence intervals for a pooled effect estimate could not be obtained in these instances.

2. The QUADAS-2 tool was used to assess the risk of bias of individual studies. Where a meta-analysis could not be conducted, individual studies reporting LR+ and LR- had equal weighting. Where ≥50% of the studies had some concerns in the risk of bias, the evidence was downgraded by one level and where ≥50% of the studies had high risk of bias the evidence was downgraded by two levels.

3. Heterogeneity (inconsistency) was assessed by visual inspection of the point estimates and confidence intervals of the included studies. Heterogeneity was independently assessed by two reviewers and discrepancies resolved. The evidence was downgraded if these varied widely between studies, for example, point estimates for some studies lying outside the CIs of other studies. Weighted subjective judgement was used to downgrade once for heterogeneity if <50% were inconsistent, or twice for heterogeneity if ≥50% were inconsistent (serious and very serious heterogeneity). The same method was used when a meta-analysis could not be conducted.

4. For ^{99m}Tc-sestamibi SPECT/CT results we decided to interpret indeterminate results reported in the included studies as malignant because in clinical practice people with indeterminate masses (often reported as equivocal in studies) following ^{99m}Tc-sestamibi SPECT/CT scan are likely to follow the same clinical pathway as malignant results. This decision was made based on committee input.

5. Some studies reported multiple observations per person. Observations from the same person are more likely to be correlated whilst observations from different people can be considered as statistically independent, therefore each person with multiple observations is considered as a cluster and measurements within a cluster are more likely to respond in a similar way (Gönen et al. 2001). It is difficult to assess the extent of the correlation and therefore combining data from clusters and observations from individual patients could lead to an over estimation of statistical significance. For this reason, data for individual lesions were analysed separately to data reported for individual people.

6. Subgroup analyses were not carried out because the included studies did not report data in a format that could be used to carry out these analyses.

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

1.1.3.1 Search methods

The searches for the effectiveness and diagnostic test accuracy evidence were run on 24/10/2024 and re-run on 15/04/2025. The following databases were searched: Cochrane CENTRAL (Wiley), Cochrane CDSR (Wiley), Embase (Ovid), Epistemonikos (Epistemonikos), Medline ALL (Ovid). Limits were applied to remove animal studies, conference abstracts, editorials, letters, news items and commentaries, as well as papers not published in the English language. Filters were used to limit to OECD countries, systematic reviews, randomised controlled trials, observational studies and diagnosis studies.

The searches for the cost effectiveness evidence were run on 30/10/2024 and re-run on 08/05/2025. The following databases were searched: Econlit (Ovid), Embase (Ovid),

International Health Technology Assessment Database (INAHTA), Medline ALL (Ovid). Limits were applied to remove animal studies, conference abstracts, editorials, letters, news items and commentaries, as well as papers not published in the English language. Filters were used to limit to OECD countries, cost utility, health state utility and cost effectiveness studies.

One search was developed to cover review I1 and review I2. 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

1.1.3.2 Protocol deviations

1. For studies that investigated the use of contrast-enhanced ultrasonography (CEUS) in the differentiation between solid masses and complex cysts the reference standard was broadened to include follow-up in addition to pathological confirmation with surgery or biopsy. The reason for this was that cystic lesions may not have a solid mass from which tissue can be taken for biopsy. People with cysts may also not undergo surgery in practice, making pathological confirmation less likely in these instances.
2. We used MetaDTA based on the R glmer package instead of the mada package due to an update to NICE methods after the protocol was written.

1.1.4 Effectiveness and diagnostic evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 6,319 references (see appendix B for the literature search strategy).

These 6,688 references were screened at title and abstract level against the review protocol, with 6,585 excluded at this level. 10% of references were screened separately by two reviewers with 99.7% agreement. Discrepancies were resolved by discussion.

The full texts of 103 references were ordered for closer inspection. Seven of these studies met the criteria for this review specified in the review protocol (appendix A). For a summary of the 7 included studies for this review see Table 3. All the included studies were diagnostic test accuracy studies, no test and treat RCTs were identified.

Seven studies met the criteria outlined in appendix A of report I1 which reviewed the evidence for CT and MRI for diagnosing renal lesions in adults with suspected renal cell carcinoma. For a summary of these studies, see report I1.

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

See section 1.1.14 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 diagnostic evidence

Table 3: Summary of studies included in the diagnostic evidence

Study details	Location /Funding	Population	Index test	Reference test	Previous imaging	Target condition definition	Risk of bias
Nicolau (2015) N= 72 Study type: prospective cohort Follow-up, median (range): 23 (23-41) months	Location: Spain Funding source: Not reported	People with an indeterminate renal nodule on a CT scan	CEUS	Pathological confirmation after surgical intervention Follow-up	CT scan	Potentially malignant (Bosniak III, IV or solid lesions) Complex cysts (Bosniak I, II, IIF)	High
Parihar (2023) N= 27 Study type: retrospective cohort Follow-up: not reported	Location: US Funding source: Not reported	People with an indeterminate solid renal lesion	99mTc-sestamibi SPECT/CT	Pathological confirmation after surgical intervention or biopsy	Contrast enhanced CT was conducted in 20 people	Malignant: clear cell RCC, papillary RCC, collision clear cell chromophobe RCC Benign: Oncocytoma, chromophobe RCC, HOCT, RCC with oncocytic features, angiomyolipoma, oncocytic renal neoplasm	High

Study details	Location /Funding	Population	Index test	Reference test	Previous imaging	Target condition definition	Risk of bias
Sheikhbahaei (2017) N= 48 Study type: retrospective cohort Follow-up: not reported	Location: US Funding source: Buerger Family Scholar Fund and the National Kidney Foundation of Maryland	People with indeterminate renal mass	99mTc-sestamibi SPECT/CT	Pathological confirmation after surgical intervention	CT, contrast-enhanced MRI, and non–contrast-enhanced MRI.	Malignant: clear cell RCC, papillary RCC, clear cell papillary RCC, unclassified RCC, chromophobe RCC Benign: oncocytoma, HOCT, angiomyolipoma	Moderate
Sistani (2021) N= 29 Study type: retrospective cohort Follow-up: not reported	Location: Canada Funding source: Ontario Health Insurance Plan	People with indeterminate renal mass	99mTc-sestamibi SPECT/CT	Pathological confirmation after surgical intervention or biopsy	CT scan	Malignant: chromophobe RCC, Clear cell RCC, Papillary RCC, Mixed papillary, clear-cell RCC Benign: oncocytoma, HOCT	High
Tzortzakakis (2022) N=52 Study type: Prospective cohort Follow-up: not reported	Location: Sweden Funding source: Supported by Sweden's innovation agency VINNOVA	People with indeterminate renal mass (T1 renal tumours)	99mTc-sestamibi SPECT/CT	Pathological confirmation after surgical intervention or biopsy	CT scan	Malignant: chromophobe RCC, Clear cell RCC, Papillary RCC, clear-cell papillary RCC, collision RCC, B-cell Lymphoma	Moderate

Study details	Location /Funding	Population	Index test	Reference test	Previous imaging	Target condition definition	Risk of bias
						Benign: oncocytoma, HOCT, metanephric adenoma, angiomyolipoma	
Viswambaram (2022) N= 74 Study type: Prospective cohort Follow-up: not reported	Location: Australia Funding source: not reported	People with indeterminate renal mass	99mTc-sestamibi SPECT/CT	Pathological confirmation after surgical intervention or biopsy	CT scan	Malignant: clear cell RCC, Papillary RCC type 1, 2 and mixed, chromophobe RCC, Squamous cell carcinoma Benign: oncocytoma, angiomyolipoma	Moderate
Yong (2024) N= 43 Study type: Retrospective cohort Follow-up median, range: 19 (2-163) months	Location: US Funding source: reported as nil	People with indeterminate renal mass. People selected based on physician judgment.	99mTc-sestamibi SPECT/CT	Pathological confirmation after surgical intervention or biopsy	CT scan	Malignant: no detail reported on specific mass types Benign: oncocytoma	Moderate

CEUS: contrast enhanced ultrasound; HOCT: hybrid oncocytic chromophobe tumour; RCC: renal cell carcinoma; SPECT: single-photon emission computed tomography

See Appendix D –Diagnostic evidencefor full evidence tables.

1.1.6 Summary of the diagnostic evidence

The interpretation of the diagnostic ability of each index test was based on the thresholds listed in Table 2**Error! Reference source not found.**. Where the positive likelihood ratio value is more than 1 it shows an increase in the probability of a positive result in a person with the condition (solid mass for CEUS and malignant mass for ^{99m}Tc-sestamibi SPECT/CT) compared to a person without. Where the negative likelihood ratio is any value less than 1 it shows a decrease in likelihood that a person with the condition (solid mass for CEUS and malignant mass for ^{99m}Tc-sestamibi SPECT/CT) will have a negative result compared to someone without the condition.

Table 4: Summary of findings for diagnostic accuracy of ^{99m}Tc-sestamibi SPECT/CT for people with suspected renal cell carcinoma (person as unit of analysis)

Number of studies	Outcome	Sample size	Effect estimate range[1]	Certainty	Interpretation of diagnostic ability
4 (Sheikhbahaei 2017, Tzortzakakis 2022, Viswambaram 2022, Yong 2024)	Diagnostic accuracy (malignant vs. benign)	222	LR + 1.62 – 4.27	VERY LOW	Slight to moderate increase in probability of disease
			LR – 0.07 – 0.25	VERY LOW	Large to very large decrease in probability of disease

LR, likelihood ratio

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

1. A bivariate meta-analysis could not be conducted as the data from the included studies did not converge, so the range has been presented for the effect estimates.

Table 5: Summary of findings for diagnostic accuracy of ^{99m}Tc-sestamibi SPECT/CT for people with suspected renal cell carcinoma (lesion as unit of analysis)

Number of studies	Outcome	Sample size	Effect estimate range[1]	Certainty	Interpretation of diagnostic ability
2 (Parihar 2023, Sistani 2021)	Diagnostic accuracy (malignant vs. benign)	56 (67 lesions)	LR + 2.17 – 16.26	VERY LOW	Moderate to very large increase in probability of disease
			LR – 0.05 – 0.18	VERY LOW	Large to very large decrease in probability of disease

LR, likelihood ratio

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

1. A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

Table 6: Summary of findings for diagnostic accuracy of CEUS for people with suspected renal cell carcinoma (lesion as unit of analysis)

Number of studies	Outcome	Sample size	Effect estimate (95% CI)	Certainty	Interpretation of diagnostic ability
1 (Nicolau 2015)	Diagnostic accuracy (solid mass vs complex cyst)	72 (83 lesions)	LR + 23.49 (6.02, 91.56)	VERY LOW	Very large increase in probability of disease
			LR – 0.06 (0.02, 0.24)	VERY LOW	Very large decrease in probability of disease

LR, likelihood ratio

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

See appendix F for full GRADE tables.

1.1.7 Economic evidence

A single literature search was conducted to identify published economic evaluations of relevance to the review questions on imaging for diagnosis of renal lesions in this guideline, which included evidence review I1 for CT and MRI and evidence review I2 (the present review) for additional imaging tests (see appendix B for the search strategy).

This search retrieved 182 studies, and based on title and abstract screening seven studies were identified as potentially relevant for either review I1 and I2 on imaging for diagnosis of renal lesions. On review of the full text, one study was included for this review, and the remaining six were excluded. For details on study selection, see economic study selection flow chart in appendix G.

1.1.7.1 Included studies

One study was included at full text review for this review question, summarised in Table 7 with further information detailed in appendix H.

1.1.7.2 Excluded studies

Six studies were excluded at full text review (see appendix J for a list of excluded economic studies at full text with reasons for exclusion).

1.1.8 Summary of included economic evidence

Table 7 Economic evidence profile

Study	Applicability and limitations	Key details	Cost (£)	Effects (QALYs)	ICER (£/QALY)	Uncertainty
Spiesecke et al. 2021 (Germany)	Partially applicable[2] Minor limitations[3]	• Interventions: diagnosis and monitoring with 1) contrast-enhanced CT (CECT) 2) contrast-enhanced MRI (CEMRI) 3) contrast-enhanced ultrasound (CEUS) • Population: 60-year old people with Bosniak 2F and 3 renal cysts • Decision tree followed by Markov for benign/malignant findings • German healthcare system perspective • Effectiveness: Meta-analysis of diagnostic accuracy. • Time horizon: 10 years	Bosniak 2F 1) £1,496 2) £1,526 3) £1,413 Bosniak 3 1) £4,207 2) £4,838 3) £3,980	Bosniak 2F 1) 8.0868 2) 8.0872 3) 8.0878 Bosniak 3 1) 8.0245 2) 8.0282 3) 8.0328	Bosniak 2F 2 vs 1: £66,999 3 vs 1: Dominant Bosniak 3 2 vs 1: £174,213 3 vs 1: Dominant	Deterministic sensitivity analysis found that diagnostic accuracy and costs of imaging and surgery had the greatest impact on the results. Probabilistic sensitivity analysis, compared with CECT; • Bosniak 2F cysts, CEMRI was more expensive in 60% of cases and more effective in 84% of cases. • Bosniak 2F cysts, CEUS was more expensive in 23% of cases and more effective in 99.9% of cases • Bosniak 3 cysts, CEMRI was more expensive in 99.9% of cases and more effective in 84% of cases. • Bosniak 3 cysts, CEUS was more expensive in 0.5% of cases and more effective in 99.9% of cases • CEUS was dominant in the probabilistic analysis.

Study	Applicability and limitations	Key details	Cost (£)	Effects (QALYs)	ICER (£/QALY)	Uncertainty
						No uncertainty was assumed for annual death rates which were considered to precisely reflect the situation.

Abbreviations: ICER=incremental cost-effectiveness ratio; QALY=Quality-adjusted life-year; LY=life year

1. Cost year 2018. Costs were converted from 2018 Euros to 2018 pound sterling using IMF Purchasing Power Parities: https://eppi.ioe.ac.uk/costconversion/default.aspx.
2. Study was only in a very specific subgroup of the population (people who have already confirmed Bosniak 2F/3 cystic renal lesions) and was in a German hospital setting with slightly different costs and discount rates.
3. 10-year time horizon may not fully capture all downstream consequences given patients enter the model at age 60.

1.1.9 Economic model

No original economic modelling was conducted for this review.

1.1.10 Unit costs

Unit costs of imaging are provided in Table 8 to aid committee deliberations around cost-effectiveness. Costs of SPECT-CT and parathyroid scan were considered to be relevant for ^{99m}Tc-sestamibi SPECT/CT.

Table 8: Unit costs of imaging

Resource	Unit costs	Source
Ultrasound <20 minute duration without contrast	£66.95	NHS Cost Collection (2024), RD40Z Ultrasound Scan with duration of less than 20 minutes without contrast
Ultrasound <20 minute duration with contrast	£53.32	NHS Cost Collection (2024), RD41z Ultrasound Scan with duration of less than 20 minutes with contrast
Ultrasound >20 minute duration without contrast	£88.18	NHS Cost Collection (2024), RD42Z Ultrasound Scan with duration of more than 20 minutes without contrast
Ultrasound >20 minute duration with contrast	£29.96	NHS Cost Collection (2024), RD43Z Ultrasound Scan with duration of more than 20 minutes with contrast
SPECT-CT of one area	£306.02	NHS Cost Collection (2024), RN04A Single Photon Emission Computed Tomography with Computed Tomography (SPECT-CT) of One Area, 19 years and over
Parathyroid scan	£460.30	NHS Cost Collection (2024), RN24Z Parathyroid Scan

HRG: healthcare resource group. SPECT: single-photon emission computed tomography. CT: computed tomography

1.1.11 Evidence statements

Economic evidence statements

One cost-utility analysis from Germany (Spiesecke et al. 2021) in adults with Bosniak 2F and 3 renal cysts found that for diagnosis and monitoring, contrast-enhanced ultrasound is potentially an effective use of NHS resources as it was both cheaper and more effective than diagnosis and monitoring with either contrast-enhanced MRI or contrast-enhanced CT imaging.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee agreed that likelihood ratios were critical measures and, sensitivity and specificity were important measures of the usefulness of the tests of interest for this review. The likelihood ratios provide information on how much more or less likely a given test result (positive or negative) is in someone with renal cell carcinoma compared to someone without it. Sensitivity and specificity would identify how well the index test would accurately identifying those with renal carcinoma and those without. Likelihood ratios were chosen as the primary measure of interest for decision making. For more detail about what information likelihood ratios provide, see the methods chapter.

The committee discussed the consequences of false positive and false negative results with additional imaging. They noted that the effects of having these results vary depending on the individual. They highlighted that there is a risk that a person will go on to have unnecessary treatment, for example surgery, after a false positive result with potentially negative effects on a person's health, in particular relating to a reduction in renal function. However, they agreed that the oncological harm associated with a false negative result is more of a concern. In these cases, there is a risk of delayed diagnosis and subsequent metastatic disease, especially where surveillance is not conducted. Whilst the committee agreed that biopsy may still be useful after these additional tests, they highlighted that this is not always carried out in practice and therefore clinical decisions are often based on the imaging results alone.

The committee also briefly discussed the clinical outcomes from test and treat studies that would be particularly important for this review. These included the need for biopsy, overall survival, and quality of life because these would provide information about the impact of receiving treatment following a positive index test. However, there were no test and treat studies identified in this review. The committee were confident that, at the early stages of disease detection, test accuracy would have an effect on clinical outcomes and therefore agreed that testing the link between test accuracy and clinical outcomes was not necessary. This, combined with the difficulty of running test and treat trials, meant the committee agreed to base their recommendations on the results of cohort studies looking at diagnostic test accuracy.

1.1.12.2 The certainty of the evidence

For 99mTc-sestamibi SPECT/CT the evidence was rated as very low certainty. The evidence was downgraded due to risk of bias using the QUADAS-2 tool. The issues with risk of bias were often due to lack of information on methods of enrolment. There were also concerns around knowledge of the index test results when interpreting the reference standard results and lack of information on the time interval between the index test and the reference standard, which could cause concerns if the disease developed over time. However, this is unlikely to have been an issue unless the interval spanned a few years. We had to assess the certainty of evidence for lesions and persons separately and it was not possible to conduct a bivariate meta-analysis due to issues with convergence and low number of studies that could be meta-analysed (see section 1.1.3 Methods and process. The evidence was downgraded for inconsistency when considering the range in the point estimates from the

individual studies and further downgraded for imprecision when the confidence intervals crossed one or more decision making thresholds.

For contrast-enhanced ultrasound (CEUS), only one study was identified (Nicolau et al., 2015). The study had a high risk of bias rating due to the exclusion of some people with an inconclusive diagnosis and a lack of information on the timing interval between the index test and reference standard and whether the reference standard results were interpreted with knowledge of the index test results. The committee noted that the data from the CEUS study included people who had received ultrasound as a baseline scan followed by CEUS, but they did not think that this would impact the results in a way that would warrant downgrading the evidence for indirectness, as they considered the initial ultrasound would not provide additional information over the CEUS. The evidence was downgraded for imprecision when the confidence intervals crossed one or more decision making thresholds.

1.1.12.3 Benefits and harms

The committee noted that the evidence from this review complemented the findings from the review on the diagnostic accuracy of imaging using contrast-enhanced CT and contrast-enhanced MRI, reported in evidence review I1. The guideline recommendations on diagnosis were based on the evidence from both reviews. The discussion below covers the recommendations on CEUS and ^{99m}Tc-sestamibi SPECT/CT that were made based on the evidence in this review, while the recommendations for other types of imaging that are used earlier in the diagnostic pathway are covered in review I1.

Contrast-enhanced ultrasound (CEUS)

The committee acknowledged the limitations of the evidence with data available from only one study with a relatively small sample size. The committee noted that the likelihood ratios showed a very large increase in the probability of having RCC given a positive test in people with a solid lesion and a very large decrease in the probability of having RCC given a negative test. They acknowledged the wide confidence intervals around the positive likelihood ratio suggesting uncertainty around the result. However, the 95% CI ranged from 6 (a large increase in probability) to 92 (a very large increase in probability) so this uncertainty around the size of effect would not affect decision making. The sensitivity and specificity of the results showed CEUS to be good at correctly identifying those with and without a solid lesion with relatively narrow confidence intervals around the estimates. The committee agreed that the diagnostic accuracy outcomes were in alignment with what is seen in practice and that the test was sufficiently accurate to be useful in practice.

The committee discussed the contrast agent used in CEUS and highlighted that it is not nephrotoxic and is therefore a good option for people with end stage renal failure where contrast agents used in other types of contrast-enhanced imaging (such as contrast enhanced CT [CECT] or contrast enhanced MRI [CEMRI]) are contraindicated or where the person has an allergy to the contrast agents used with these imaging modalities. The committee also noted that the ultrasound contrast agent is inexpensive and can be used with any modern ultrasound machine. The committee highlighted that for some people MRI may not be compatible, for example due to metal being in the body and if a person is unable to hold their breath. Based on these points and the evidence for the diagnostic accuracy of CEUS in differentiating between complex cysts and solid lesions, they agreed that for people who cannot have CECT or MRI (with or without contrast), CEUS could be useful in helping to determine the type of lesion (whether it is solid or cystic) and cyst characteristics. The

committee also noted that in some cases uncertainty around the type of lesion can remain after CECT or MRI (with or without contrast) or both types of imaging and that CEUS could provide information to help resolve this uncertainty. They also noted that MRI may be unavailable in some areas or have long waiting times, so they included the options to have CEUS after CECT or MRI or after both types of imaging to allow more flexibility in the diagnostic imaging pathway. Due to the limitations in the evidence identified, the committee made a weaker consider recommendation to reflect these points.

When considering both this review and the complementary evidence for other imaging (CT and MRI) that is recommended for use earlier in the diagnostic pathway in review I1, they agreed that it would be helpful to know which combinations and sequences of imaging might be most accurate and cost effective in differentiating between benign and malignant tumours. Therefore, they made a research recommendation covering this area. They also included biopsy in this research recommendation because it forms an important part of the diagnostic pathway.

The committee discussed the next steps following the identification of a solid lesion on CEUS and highlighted that the decision to do a biopsy or proceed to treatment would depend on the person and the size of the lesion, and that recommendations elsewhere in the guideline cover biopsy and management (for more information see evidence review J on renal biopsy and evidence reviews A, B and C on the management of localised or locally advanced RCC).

^{99m}Tc-sestamibi SPECT/CT

The committee examined the diagnostic accuracy outcome results for ^{99m}Tc-sestamibi SPECT/CT. For analysis by person, the likelihood ratios showed a slight-to-moderate increase in the probability of a positive test and a large-to-very large decrease in the probability of RCC given a negative test (Table 4). For the analysis by lesion numbers the likelihood ratios showed a moderate-to-very large increase in the probability of a positive test and a large-to-very large decrease in the probability of a negative test in those with a malignant lesion compared to those without and the evidence was very low certainty (

Table 5). The committee agreed that the sensitivity and specificity results were consistent with what they would expect from practice and noted that they also see reduced specificity with increased sensitivity.

The committee discussed the position of ^{99m}Tc-sestamibi SPECT/CT in the diagnostic pathway for renal cell carcinoma (RCC) and who would be suitable for this type of imaging. They noted that if a cystic lesion is suspected then CEUS would provide useful information to help identify and characterise the type of lesions. They agreed that ^{99m}Tc-sestamibi SPECT/CT could be used to provide information about whether a lesion is likely to be an oncocytoma (and so benign) or malignant where uncertainty remains after other imaging using CECT or MRI (with or without contrast). However, they noted that there can be overlap in the appearance of oncocytoma and chromophobe RCC. They highlighted that ^{99m}Tc-sestamibi SPECT/CT would be useful for people in whom biopsy is not possible, for example due to the position of the tumour or use of certain medication such as anticoagulants where there would be a higher risk of bleeding. However, where a biopsy is possible this would provide more accurate information about the type of lesion and characteristics and should be promoted over this type of imaging, although it was acknowledged that some people may decline biopsy. Based on the results and their discussions, the committee recommended that that 99mTc-sestamibi SPECT/CT imaging could be considered after CT or MRI in cases where knowledge of whether a person has an oncocytic lesion (including oncocytoma or chromophobe RCC) would change management and where biopsy was not an option or where a person does not want to have a biopsy.

1.1.12.4 Cost effectiveness and resource use

One economic evaluation was identified which addressed the cost-effectiveness of additional imaging tests for differentiating renal lesions. The study was only in a subset of the target population (Bosniak 2F and 3 renal cysts), however the conclusion that CEUS is likely to be cost-effective for determining malignancy, being both more effective and less costly than CECT and CEMRI, broadly supports the recommendation on using CEUS after initial imaging to resolve remaining uncertainty after initial imaging.

The committee considered the unit costs of imaging when making their recommendations and noted that the costs reported in Table 8 from NHS Cost Collection did not reflect clinical reality, as ultrasound with contrast is expected to be more expensive than without contrast, although it is unclear why this is not the case in the reference costs publication.

The committee recommended that CEUS should be considered if there is remaining uncertainty after initial imaging, and although this may increase the numbers of CEUS scans, the additional costs are expected to be offset by the benefits of guiding more appropriate treatment which would reduce unnecessary treatment costs and avoid negative patient outcomes such as reduced effectiveness or adverse events.

There was some uncertainty in the cost and availability of 99mTc-sestamibi SPECT/CT, and there was no relevant economic evidence identified for this decision problem. The clinical codes relating to 99mTc-sestamibi SPECT/CT were obtained from the thyroid cancer clinical guideline (NG230), and their relevance confirmed with the committee.

The committee limited the recommendation of 99mTc-sestamibi SPECT/CT to a specific set of cases, when biopsy is not a suitable option, or for investigation for an oncocytic lesion. Combined with a weaker strength of the recommendation, the resource implications are likely to be moderate. It is expected that this recommendation would also help to guide more

appropriate treatment for the individual in those cases, reducing unnecessary costs and avoiding negative patient outcomes.

The committee discussed the availability of CEUS and highlighted that whilst CEUS only requires an ultrasound scanner and a contrast agent its use is limited by the availability of trained radiologists to conduct the scan. As a result, it may only be available in specialist centres, and this could limit its use in practice unless more radiologists are trained to carry out this type of imaging. If wider use of CEUS is promoted, then there may be additional training required for the workforce.

There was some concern about the availability of ^{99m}Tc-sestamibi SPECT/CT but it was noted that although it is not used regularly in practice for people with suspected RCC, the SPECT/CT scanner is available in centres across the UK. It is commonly used in current practice for the identification and localisation of parathyroid adenomas, and to detect perfusion abnormality in the heart. In addition, the committee did not foresee large numbers of people requiring this type of scan and noted that 99mTc-sestamibi is a relatively inexpensive radiopharmaceutical.

1.1.12.5 Other factors the committee took into account

The committee discussed the definition of the term “indeterminate” which is used in some of the included studies for lesions that require further imaging with CEUS or ^{99m}Tc-sestamibi SPECT/CT**.** The committee agreed that using the term “indeterminate” could be confusing as for some healthcare professionals it could be used to refer to a lesion where it was unclear if the person had cancer or not whilst other healthcare professionals may use the term to refer to difficulty in establishing enhancement or if a lesion is solid or cystic. The committee agreed to not use the term “indeterminate” when referring to lesions that are unclear.

The committee discussed whether any specific equality issues applied to additional imaging for diagnosis of RCC and whether any specific population groups could be disadvantaged by the recommendations. Most of the issues identified in the equality and health inequalities assessment (EHIA) were societal in nature and focused on non-kidney cancer or imaging specific issues to do with access for populations such as older adults, disabled people and people with lower socio-economic status. However, the committee agreed that CEUS is a good option for people with very high weight because it does not have an upper weight limit as is the case for CT and MRI scanners. In these cases where a CT or MRI is not possible, the committee agreed that the person with suspected RCC should have access to CEUS instead and that the recommendation they had drafted above allowed for this scenario.

The committee also emphasised the importance of taking a person-centred approach by including the person with suspected RCC in decision-making and informing them about imaging results in a timely manner (see evidence review I1 for more information about these discussions).

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.5 to 1.2.6 and the research recommendation on combinations and sequences of diagnostic approaches.

1.1.14 References – included studies

Nicolau, Carlos, Bunesch, Laura, Pano, Blanca et al. (2015) Prospective evaluation of CT indeterminate renal masses using US and contrast-enhanced ultrasound. Abdominal imaging 40(3): 542-51

Parihar, Ashwin Singh, Mhlanga, Joyce, Ronstrom, Carrie et al. (2023) Diagnostic Accuracy of 99mTc-Sestamibi SPECT/CT for Characterization of Solid Renal Masses. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 64(1): 90-95

Sheikhbahaei, Sara, Jones, Christopher S, Porter, Kristin K et al. (2017) Defining the Added Value of 99mTc-MIBI SPECT/CT to Conventional Cross-Sectional Imaging in the Characterization of Enhancing Solid Renal Masses. Clinical nuclear medicine 42(4): e188-e193

Sistani, Golmehr, Bjazevic, Jennifer, Kassam, Zahra et al. (2021) The value of 99mTc-sestamibi single-photon emission computed tomography-computed tomography in the evaluation and risk stratification of renal masses. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 15(6): 197-201

Tzortzakakis, A., Papathomas, T., Gustafsson, O. et al. (2022) 99mTc-Sestamibi SPECT/CT and histopathological features of oncocytic renal neoplasia. Scandinavian Journal of Urology 56(56): 375-382

Viswambaram, Pravin, Swarbrick, Nicole, Picardo, Alarick et al. (2022) Technetium-99 m-sestamibi single-photon emission computerised tomography (CT)/CT in the prediction of malignant versus benign small renal masses. BJU international 130suppl3: 23-31

Yong, Courtney, Tong, Yan, Tann, Mark et al. (2024) The impact of sestamibi scan on clinical decision-making for renal masses: An observational single-center study. Indian journal of urology : IJU : journal of the Urological Society of India 40(3): 151-155

1.1.14.2 Economic

Spiesecke, Paul, Reinhold, Thomas, Wehrenberg, Yano et al. (2021) Cost-effectiveness analysis of multiple imaging modalities in diagnosis and follow-up of intermediate complex cystic renal lesions. BJU international 128(5): 575-585

1.1.15 References – other

Gönen M, Panageas KS, Larson SM. (2001) Statistical issues in analysis of diagnostic imaging experiments with multiple observations per patient. Br J Radiol. 221(3): 763-7

MetaDTA tool is described in the below papers:

Patel A, Cooper NJ, Freeman SC, Sutton AJ. Graphical enhancements to summary receiver operating charcateristic plots to facilitate the analysis and reporting of meta-analysis of diagnostic test accuracy data. Research Synthesis Methods 2020, https://doi.org/10.1002/jrsm.1439.

Freeman SC, Kerby CR, Patel A, Cooper NJ, Quinn T, Sutton AJ. Development of an interactive web-based tool to conduct and interrogate meta-analysis of diagnostic test

accuracy studies: MetaDTA. BMC Medical Research Methodology 2019; 19: 81 which can be accessed at MetaDTA version 1.27.

NHS England. National Cost Collection for the NHS 2023/24. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/

Appendices

Appendix A – Review protocols

Diagnostic accuracy review protocol for diagnosis and assessment of renal cell carcinoma: additional imaging for people who have had CT or MRI

Table 9: Review protocol

ID	Field	Content
1.	Review title	Accuracy and cost effectiveness of additional imaging tests for diagnosing renal lesions in adults who have had CT or MRI for suspected RCC.
2.	Review question	What is the clinical and cost effectiveness of 99mTc-sestamibi SPECT/CT compared with contrast-enhanced ultrasound for differentiating and managing renal lesions in adults with suspected renal cell carcinoma? 2. In adults with suspected renal cell carcinoma, what is the diagnostic accuracy and cost effectiveness of: • 99mTc-sestamibi SPECT/CT • contrast-enhanced ultrasound for differentiating renal lesions?
3.	Objective	To evaluate and compare the clinical effectiveness, accuracy and cost effectiveness of additional imaging tests for differentiating benign from malignant renal lesions or complex cysts in adults with suspected RCC who have had CT or MRI imaging.
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 • 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 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	Suspected renal cell carcinoma
6.	Population	Adults (18 years or over) with suspected RCC on CT/MRI Suspected RCC refers to cases where there are diagnostic findings on CT or MRI suggestive of RCC but where a definitive diagnosis has not yet been made.
7.	Index test	• ^{99m}Tc-sestamibi SPECT/CT for differentiating between benign and malignant renal lesions • Contrast-enhanced ultrasonography (US) for differentiating between solid masses and complex cysts
8.	Reference standard	Pathological confirmation of RCC from surgery or biopsy
9.	Types of study to be included	• Diagnostic accuracy cross-sectional studies and cohort studies. • Systematic reviews of diagnostic accuracy cross-sectional studies. • Where there are no cross-sectional or cohort studies identified, case-control studies will be included. • Test and treat RCTs and SRs of test and treat RCTs
10.	Other exclusion criteria	• Diagnostic accuracy studies that do not report sufficient information to allow a 2*2 table (TP, FP, TN, FN) to be constructed will be excluded
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 the NHS. Stakeholders identified this gap, and NICE was commissioned to develop a guideline on kidney cancer by NHSE. A timely and accurate diagnosis of RCC is of great significance to guide treatment and improve patient's outcomes. Various non-invasive imaging approaches are options for supplementary imaging

		tests for differentiating renal masses and complex cysts after initial imaging with CT or MRI. These imaging techniques include: • contrast enhanced ultrasound to differentiate whether a lesion is solid or cystic and • sestamibi scans to differentiate whether a mass is benign or malignant. Therefore, an evidence review is required to evaluate the clinical effectiveness, diagnostic accuracy and cost effectiveness of these supplementary imaging tests.

12.	Outcomes	Diagnostic accuracy outcome measures:
		• Sensitivity and specificity
		• Positive and negative likelihood ratios
		
		Clinical outcomes (for test and treat studies):
		• Need for biopsy (dichotomous outcome)
		• Overall survival (time to event data)
		Some studies may report overall survival as death or mortality. These will be extracted as proxy outcomes where survival data is not reported in the studies.
		• Quality of life using:
		  ○ EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30; continuous or dichotomous outcome)
		  ○ EuroQol-5 dimensions (EQ-5D; continuous or dichotomous outcome)
		
		Minimal important differences
		Any statistically significant difference will be used for the following outcomes:
		• Need for surgical or non-surgical intervention
		• Need for biopsy
		• 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 diagnostic test studies will be assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2) 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 test and treat 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
15.	Strategy for data synthesis	Diagnostic test accuracy (DTA) data will be used to generate a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not). Where possible, meta-analyses of diagnostic accuracy data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 2.1 (Deeks et al. 2022). When five or more studies are available for all included strata, a bivariate model will be fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data were not available (2-4 studies), separate independent pooling will be performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using R. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010). Random-effects models (der Simonian and Laird) will be fit for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). Evidence from diagnostic accuracy studies will be initially rated as high-certainty, and then downgraded according to the standard GRADE criteria. GRADE will be carried out on the LR results, but the results for sensitivity and specificity will also be presented. Where data can be disambiguated it will be separated into the subgroups identified in section 16 (below).

		In all cases, the downstream effects of diagnostic accuracy on patient-important outcomes will be considered based on the evidence. If there is no or limited evidence for downstream effects of diagnostic accuracy, considerations for this will be explicitly discussed during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. For RCT evidence: 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 certainty of the outcomes. All outcomes in this review which come from RCTs, and systematic reviews will be rated as high certainty initially and downgraded from this point. 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: • age, • tumour size, • location and complexity of the tumours, • renal function at baseline, and • performance status of the person at baseline (e.g., ECOG and Karnofsky).
17.	Type and method of review	X Intervention Diagnostic Prognostic Qualitative

		Epidemiologic Service Delivery Other (please specify)		
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	November 2014		
21.	Anticipated completion date	March 2026		
22.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	X	X
		Piloting of the study selection process	X	X
		Formal screening of search results against eligibility criteria	X	X
		Data extraction	X	X
		Risk of bias (quality) assessment	X	X
		Data analysis	X	X
23.	Named contact	**5a. Named contact** Centre for Guidelines, NICE **5b Named contact e-mail** kidneycancerguideline@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team.		
24.	Review team members	From the Guideline Development Team: • Steve Sharp, Technical adviser • Marie Harrisingh, Technical adviser • Sarah Boyce, Senior technical analyst • Fernando Zanghelini, Technical analyst • Olivia Crane, Senior technical analyst • Lucy Beggs, Health economics adviser • Hannah Tebbs, Health economist • Yuanyuan Zhang, Health economist • Amy Finnegan, Senior Information specialist		
25.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team which receives funding from NICE.		
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (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, partial nephrectomy, radical nephrectomy
32.	Details of existing review of same topic by same authors	Not applicable
33.	Current review status	X Ongoing Completed but not published 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

Table 10: Economic review protocol

ID	Field	Content

1.	Review titles	I1: Cost effectiveness of CT and MRI for diagnosing renal masses in adults with suspected renal cell carcinoma I2: Cost effectiveness of additional imaging tests for diagnosing renal masses in adults who have had CT or MRI for suspected renal cell carcinoma
2.	Objective	To identify economic studies for the review to evaluate and compare the accuracy and cost effectiveness of additional imaging tests for differentiating benign from malignant renal masses or complex cysts in adults with suspected RCC who have had CT or MRI imaging
3.	Inclusion criteria	• Populations, interventions and comparators as specified in the diagnostic accuracy 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.
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 RCC. • Studies only focussing on productivity losses or gains.
5.	Search strategy	An economic study search will be undertaken using question-specific terms and an 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
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.

1

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 previous review questions for this guideline. The stage terms were removed from this version of the population.

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

Randomised control trial filters:

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 e al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ, 330, 1179-1183.

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.

Diagnosis filter:

The Medline and Embase searches were limited to diagnosis evidence using the optimal filter. Additional terms were added to the filter.

Haynes RB, Wilczynski NL. Optimal search strategies for retrieving scientifically strong studies of diagnosis from MEDLINE: analytical survey. *BMJ*. 2004;328:1040-2.

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.

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

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 searches documented in this appendix covered both review I1 and review I2.

In Medline and Embase, for the clinical searches, the strategy was split into two. The first set searched for population and intervention on title only, without applying study limits. This was

used to retrieve relevant diagnostic studies that were not identified by the search filters. The second part of the search limited the population and intervention (on title and abstract) by study filters (randomised controlled trials, diagnostic studies and the amended observational filter). Both sets were combined using OR at the end of the search. For databases where this approach was not used, the population terms were searched for on title and abstract. In Epistemonikos, the search was limited to retrieving systematic reviews.

The population terms have been used throughout the guideline. For this review question 'stage' was removed from the free-text terms to reduce results of kidney disease, which is out of scope of this guideline.

To manage the total number of results retrieved and improve the precision of the search, subject headings were focused. This approach was taken as the risk of missing a relevant paper was balanced by the searching for the population and intervention on title only.

The observational filter was amended to only identify studies that were in scope. The focus was on cohort and cross-sectional studies.

The population and intervention sets picked up all 10 of the test papers identified. 1 test paper was not retrieved by the study filters.

Clinical searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	24/10/2024	Wiley	Issue 10 of 12, October 2024	459
Cochrane Database of Systematic Reviews (CDSR)	24/10/2024	Wiley	Issue 10 of 12, October 2024	1
Embase	24/10/2024	Ovid	1974 to 2024 October 23	4856
Epistemonikos	24/10/2024	Epistemonikos	N/A	228
MEDLINE ALL	24/10/2024	Ovid	1946 to October 23, 2024	4343

Re-run search results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	15/04/2025	Wiley	Issue 3 of 12, March 2025	444
Cochrane Database of Systematic Reviews (CDSR)	15/04/2025	Wiley	Issue 3 of 12, March 2025	1
Embase	15/04/2025	Ovid	1974 to 2025 April 14	5149
Epistemonikos	15/04/2025	Epistemonikos	n/a	256
MEDLINE ALL	15/04/2025	Ovid	1946 to April 14, 2025	4629

CDSR – the 1 record found was not imported into EPPI as it was a duplicate of the record found in the original search.

Search strategy history

Database name: CDSR and CENTRAL

Searches:
#1 [mh "Kidney Neoplasms"] 1998
#2 (Kidney* NEAR/2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*)):ti,ab,kw 3397
#3 (collecting-duct* NEAR/2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*)):ti,ab,kw 15
#4 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*):ti,ab,kw 4208
#5 (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 tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*)):ti,ab,kw 115
#6 {OR #1-#5} 5641
#7 [mh ^"tomography, emission-computed"] or [mh ^"tomography, emission-computed, single-photon"] or [mh ^"tomography, x-ray computed"] or [mh ^"single photon emission computed tomography computed tomography"] 8317
#8 (CAT NEXT (electron-beam* or examination* or imag* or scan* or x ray*)):ti,ab,kw 37
#9 ((comput* NEAR/3 tomogra*) or (CT not PET)):ti,ab,kw 98571
#10 [mh "Magnetic Resonance Imaging"] 13155
#11 (magnet* resonance or MRI):ti,ab,kw 53567

Searches:
#12 ((magnet* or MR) NEXT (examination* or imag* or scan* or tomograph* or spectroscop* or multiparametric*)):ti,ab,kw 2439
#13 (contrast-enhanc* or contrastenhanc* or CEUS or SPECT or SPECTs or sestamibi* or mibi):ti,ab,kw 6209
#14 {OR #7-#13} 143378
#15 #6 and #14 in Cochrane Reviews 1
#16 #6 and #14 in Trials 781
#17 "conference":pt or (clinicaltrials or trialsearch):so 784063
#18 #16 not #17 459

1 **Database name: Embase**

Searches
1 (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. (5957)
2 (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. (316)
3 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti. (62148)
4 (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. (321)
5 or/1-4 (68066)
6 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti. (257)
7 ((comput* adj3 tomogra*) or (CT not PET)).ti. (230658)
8 (magnet*-resonance or MRI).ti. (253806)
9 ((magnet* or MR) adj (examination* or imag* or scan* or tomograph* or spectroscop* or multiparametric*)).ti. (30700)
10 (contrast-enhanc* or contrastenhanc* or CEUS or SPECT or SPECTs or sestamibi* or mibi).ti. (52326)
11 5 and (or/6-10) (2465)
12 nonhuman/ not (human/ and nonhuman/) (5553494)
13 11 not 12 (2457)
14 limit 13 to english language (2201)
15 14 not (letter or editorial).pt. (2143)
16 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (6047975)
17 15 not 16 (1696)
18 exp *kidney tumor/ (102833)
19 (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. (24619)

Searches
20 (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. (759)
21 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti,ab. (110461)
22 (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. (1254)
23 or/18-22 (155233)
24 *computer assisted emission tomography/ or *computer assisted tomography/ or *emission tomography/ or *single photon emission computed tomography/ or *x-ray computed tomography/ or *single photon emission computed tomography-computed tomography/ (178240)
25 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti,ab. (2031)
26 ((comput* adj3 tomogra*) or (CT not PET)).ti,ab. (1007697)
27 *nuclear magnetic resonance imaging/ (224007)
28 (magnet*-resonance or MRI).ti,ab. (936241)
29 ((magnet* or MR) adj (examination* or imag* or scan* or tomograph* or spectroscop*)).ti,ab. (103836)
30 (contrast-enhanc* or contrastenhanc* or CEUS).ti,ab,kw. (100173)
31 (SPECT or SPECTs or sestamibi* or mibi).ti,ab,kw. (66201)
32 or/24-31 (1906701)
33 23 and 32 (20425)
34 nonhuman/ not (human/ and nonhuman/) (5553494)
35 33 not 34 (20097)
36 limit 35 to english language (17084)
37 36 not (letter or editorial).pt. (16982)
38 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (6047975)
39 37 not 38 (10146)
40 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

Searches
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/ (1820274)
41 exp "organisation for economic co-operation and development"/ (3207)
42 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/ (3941952)
43 european union/ (32855)
44 developed country/ (36519)
45 or/41-44 (3977397)
46 40 not 45 (1658091)
47 39 not 46 (10073)
48 Clinical study/ (167953)
49 Case control study/ (225527)
50 Retrospective study/ (1702185)
51 comparative study/ (1085243)
52 Prospective study/ (946412)
53 Randomized controlled trials/ (283943)
54 52 not 53 (934752)
55 Cohort analysis/ (1235615)
56 cohort analy$.tw. (22274)
57 (Cohort adj (study or studies)).tw. (532832)
58 (Case control$ adj (study or studies)).tw. (184830)
59 (cross sectional adj (study or studies)).tw. (393316)
60 case series.tw. (163043)
61 prospective.tw. (1195904)
62 retrospective.tw. (1405044)
63 or/48-52,54-62 (5591422)
64 sensitiv*.tw. (2227361)
65 diagnostic accuracy.sh. (328996)
66 diagnostic.tw. (1341646)
67 ((likelihood adj ratio*) or lr or plr or nlr).ti,ab. (88625)
68 or/64-67 (3514049)
69 random:.tw. (2135134)
70 placebo:.mp. (547843)

Searches	
71	double-blind:.tw. (257069)
72	or/69-71 (2421168)
73	63 or 68 or 72 (10129959)
74	47 and 73 (4337)
75	(17 not 46) or 74 (4856)

1 Database name: Epistemonikos

Searches
(title:((kidney* AND (cancer* OR carcinoma* OR carcinosarcoma* OR adenocarcino* OR neoplas* OR tumor* OR tumour* OR mass OR metastat* OR malignan* OR sarcoma* OR parenchyma*)) OR (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 (renal-cell* OR rcc OR ccrcc OR renal-mass* OR (renal AND mass*) OR "renal-tumour" OR "renal-tumours" OR "renal tumour" OR "renal tumours" OR "renal-tumor" OR "renal-tumours" OR "renal tumor" OR "renal tumors" OR "grawitz-tumour" OR "grawitz-tumours" OR "grawitz tumour" OR "grawitz tumours" OR "grawitz-tumor" OR "grawitz-tumors" OR "grawitz tumor" OR "grawitz tumors" OR hypernephroma* OR nephrocarcinoma*) OR (kidney* AND (transitional-cell* OR (transitional AND 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:((kidney* AND (cancer* OR carcinoma* OR carcinosarcoma* OR adenocarcino* OR neoplas* OR tumor* OR tumour* OR mass OR metastat* OR malignan* OR sarcoma* OR parenchyma*)) OR (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 (renal-cell* OR rcc OR ccrcc OR renal-mass* OR (renal AND mass*) OR "renal-tumour" OR "renal-tumours" OR "renal tumour" OR "renal tumours" OR "renal-tumor" OR "renal-tumours" OR "renal tumor" OR "renal tumors" OR "grawitz-tumour" OR "grawitz-tumours" OR "grawitz tumour" OR "grawitz tumours" OR "grawitz-tumor" OR "grawitz-tumors" OR "grawitz tumor" OR "grawitz tumors" OR hypernephroma* OR nephrocarcinoma*) OR (kidney* AND (transitional-cell* OR (transitional AND 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:((cat AND ("electron-beam" OR "electron-beams" OR "electron beam" OR "electron beams" OR examination* OR imag* OR scan* OR x ray*)) OR ((comput* AND tomogra*) OR (ct NOT pet)) OR (magnet* resonance OR mri) OR ((magnet* OR mr) AND (examination* OR imag* OR scan* OR tomograph* OR spectroscop* OR multiparametric*)) OR ((contrast AND enhance*) OR contrastenhanc* OR ceus OR spect OR spects OR sestamibi* OR mibi)) OR abstract:((cat AND ("electron-beam" OR "electron-beams" OR "electron beam" OR "electron beams" OR examination* OR imag* OR scan* OR x ray*)) OR ((comput* AND tomogra*) OR (ct NOT pet)) OR (magnet* resonance OR mri) OR ((magnet* OR mr) AND (examination* OR imag* OR scan* OR tomograph* OR spectroscop* OR multiparametric*)) OR ((contrast AND enhance*) OR contrastenhanc* OR ceus OR spect OR spects OR sestamibi* OR mibi))) Limited to systematic reviews

1 **Database name: Medline ALL**

Searches
1 (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. (4893)
2 (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. (235)
3 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti. (43585)
4 (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. (213)
5 or/1-4 (48484)
6 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti. (209)
7 ((comput* adj3 tomogra*) or (CT not PET)).ti. (173368)
8 (magnet*-resonance or MRI).ti. (189240)
9 ((magnet* or MR) adj (examination* or imag* or scan* or tomograph* or spectroscop* or multiparametric*)).ti. (25364)
10 (contrast-enhanc* or contrastenhanc* or CEUS or SPECT or SPECTs or sestamibi* or mibi).ti. (35846)
11 5 and (or/6-10) (1802)
12 animals/ not humans/ (5235447)
13 11 not 12 (1794)
14 limit 13 to english language (1670)
15 limit 14 to (letter or historical article or comment or editorial or news or case reports) (272)
16 14 not 15 (1398)
17 exp *Kidney Neoplasms/ (75451)
18 (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. (16705)
19 (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. (507)
20 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti,ab. (73582)
21 (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. (877)
22 or/17-21 (111768)
23 *tomography, emission-computed/ or *tomography, emission-computed, single-photon/ or *tomography, x-ray computed/ or *single photon emission computed tomography computed tomography/ (154481)
24 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti,ab. (1326)
25 ((comput* adj3 tomogra*) or (CT not PET)).ti,ab. (665236)
26 exp *Magnetic Resonance Imaging/ (212124)
27 (magnet*-resonance or MRI).ti,ab. (632082)

Searches
28 ((magnet* or MR) adj (examination* or imag* or scan* or tomograph* or spectroscop*)).ti,ab. (75776)
29 (contrast-enhanc* or contrastenhanc* or CEUS).ti,ab,kw. (69572)
30 (SPECT or SPECTs or sestamibi* or mibi).ti,ab,kw. (38746)
31 or/23-30 (1311928)
32 22 and 31 (12493)
33 animals/ not humans/ (5235447)
34 32 not 33 (12273)
35 limit 34 to english language (10095)
36 limit 35 to (letter or historical article or comment or editorial or news or case reports) (3793)
37 35 not 36 (6302)
38 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/ (1377466)
39 "organisation for economic co-operation and development"/ (633)
40 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/ (3603817)
41 european union/ (18233)
42 developed countries/ (21648)
43 or/39-42 (3620388)

Searches	
44	38 not 43 (1285607)
45	37 not 44 (6246)
46	exp Case-Control Studies/ (1546412)
47	exp Cohort Studies/ (2664320)
48	Cross-Sectional Studies/ (518920)
49	Comparative Study.pt. (1930436)
50	case control$.tw. (170694)
51	(cohort adj (study or studies)).tw. (370112)
52	cohort analy$.tw. (13776)
53	prospective.tw. (778770)
54	longitudinal.tw. (357872)
55	retrospective.tw. (848949)
56	cross sectional.tw. (588897)
57	or/46-56 (5709379)
58	(sensitiv: or predictive value:).mp. or accurac:.tw. (2769213)
59	((likelihood adj ratio*) or lr or plr or nlr).ti,ab. (60268)
60	diagnos*.ti. (728709)
61	or/58-60 (3379331)
62	exp Randomized Controlled Trial/ (625616)
63	randomi?ed.mp. (1148239)
64	placebo.mp. (261245)
65	or/62-64 (1216851)
66	57 or 61 or 65 (9049180)
67	45 and 66 (4059)
68	16 or 67 (4346)
69	(16 not 44) or 67 (4343)

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Econlit	30/10/2024	Ovid	1886 to October 24, 2024	1
Embase	30/10/2024	Ovid	1974 to 2024 October 29	141
International Health Technology Assessment	30/10/2024	https://database.inahta.org/	n/a	5

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Database from INAHTA				
Medline ALL	30/10/2024	Ovid	1946 to October 29, 2024	110

Re-run search results

1

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
EconLit	08/05/2025	Ovid	1886 to May 01, 2025	1
Embase	08/05/2025	Ovid	1974 to 2025 May 07	151
International Health Technology Assessment Database from INAHTA	08/05/2025	https://database.inahta.org/	n/a	130
MEDLINE	08/05/2025	Ovid	1946 to May 07, 2025	113

2 **Search strategy history**

3 **Database name: Econlit**

Searches
1 (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. (8)
2 (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 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti,ab. (25)
4 (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 (33)
6 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti,ab. (2)
7 ((comput* adj3 tomogra*) or (CT not PET)).ti,ab. (257)

Searches
8 (magnet*-resonance or MRI).ti,ab. (215)
9 ((magnet* or MR) adj (examination* or imag* or scan* or tomograph* or spectroscop*)).ti,ab. (3)
10 (contrast-enhanc* or contrastenhanc* or CEUS).ti,ab. (6)
11 (SPECT or SPECTs or sestamibi* or mibi).ti,ab. (5)
12 or/6-11 (469)
13 5 and 12 (1)

Database name: Embase

Searches
1 exp *kidney tumor/ (102891)
2 (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. (24640)
3 (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. (759)
4 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti,ab. (110502)
5 (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. (1257)
6 or/1-5 (155311)
7 *computer assisted emission tomography/ or *computer assisted tomography/ or *emission tomography/ or *single photon emission computed tomography/ or *x-ray computed tomography/ or *single photon emission computed tomography-computed tomography/ (178422)
8 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti,ab. (2030)
9 ((comput* adj3 tomogra*) or (CT not PET)).ti,ab. (1008747)
10 *nuclear magnetic resonance imaging/ (224224)
11 (magnet*-resonance or MRI).ti,ab. (937217)
12 ((magnet* or MR) adj (examination* or imag* or scan* or tomograph* or spectroscop*)).ti,ab. (103890)
13 (contrast-enhanc* or contrastenhanc* or CEUS).ti,ab,kw. (100307)
14 (SPECT or SPECTs or sestamibi* or mibi).ti,ab,kw. (66228)
15 or/7-14 (1908638)
16 6 and 15 (20442)
17 nonhuman/ not (human/ and nonhuman/) (5557871)
18 16 not 17 (20115)
19 limit 18 to english language (17101)
20 19 not (letter or editorial).pt. (16999)
21 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (6052334)
22 20 not 21 (10159)
23 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

Searches
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/ (1822220)
24 exp "organisation for economic co-operation and development"/ (3211)
25 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/ (3942805)
26 european union/ (32876)
27 developed country/ (36524)
28 or/24-27 (3978273)
29 23 not 28 (1659918)
30 22 not 29 (10085)
31 cost utility analysis/ (13284)
32 quality adjusted life year/ (38688)
33 cost*.ti. (205642)
34 (cost* adj2 utilit*).tw. (13710)
35 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (415968)
36 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (71764)
37 (qualit* adj2 adjust* adj2 life*).tw. (29556)
38 QALY*.tw. (28951)

Searches
39 (incremental* adj2 cost*).tw. (30868)
40 ICER.tw. (14273)
41 utilities.tw. (16149)
42 markov*.tw. (43081)
43 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (77461)
44 ((utility or effective*) adj2 analys*).tw. (40811)
45 (willing* adj2 pay*).tw. (16210)
46 (EQ5D* or EQ-5D*).tw. (28843)
47 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (5944)
48 (european* adj2 quality adj3 ("5" or five)).tw. (1118)
49 or/31-48 (681931)
50 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (29673)
51 (illness state$1 or health state$1).ti,ab,kf. (15845)
52 (hui or hui1 or hui2 or hui3).ti,ab,kf. (3457)
53 (multiattribute$ or multi attribute$).ti,ab,kf. (1720)
54 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (35081)
55 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or euroqol or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. (35022)
56 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. (10052)
57 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (48567)
58 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (3824)
59 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (36357)
60 quality of life/ and ec.fs. (69255)
61 quality of life/ and (health adj3 status).ti,ab,kf. (22882)
62 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ (7315)
63 or/50-62 (252273)
64 Health economics/ (36874)
65 exp health care cost/ (360061)
66 exp Fee/ (45826)
67 exp Budget/ (35304)
68 Funding/ (82648)
69 budget*.ti,ab. (50554)
70 (economic* or pharmaco?economic*).ti. (81597)
71 (price* or pricing*).ti,ab. (78919)
72 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. (314627)
73 (financ* or fee or fees).ti,ab. (253399)
74 (value adj2 (money or monetary)).ti,ab. (4398)

Searches	
75	or/64-74 (1069430)
76	49 or 63 or 75 (1500970)
77	30 and 76 (141)

Database name: INAHTA

Searches		
#1	"Kidney Neoplasms"[mhe]	129
#2	((kidney* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*)))	51
#3	(("collecting duct" or "collecting ducts") AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*))	1
#4	("renal cell" or "renal cells" or rcc or ccrcc or renal-mass* or "renal tumor" or "renal tumors" or "renal tumours" or "renal tumour" or "grawitz tumor" or "grawitz tumors" or "grawitz tumour" or "grawitz tumours" or hypernephroma* or nephrocarcinoma*)	115
#5	(kidney* AND ("transitional cell" or "transitional cells" or cell or urothelial* or duct or advanc*) AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*))	22
#6	((kidney* AND ("transitional cell" or "transitional cells" or cell or urothelial* or duct or advanc*) AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*))) OR (("renal cell" or "renal cells" or rcc or ccrcc or renal-mass* or "renal tumor" or "renal tumors" or "renal tumours" or "renal tumour" or "grawitz tumor" or "grawitz tumors" or "grawitz tumour" or "grawitz tumours" or hypernephroma* or nephrocarcinoma*)) OR ((("collecting duct" or "collecting ducts") AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*))) OR (((kidney* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*)))) OR ("Kidney Neoplasms"[mhe])	172
#7	"Tomography Emission-Computed"[mh]	116
#8	"Tomography Emission-Computed Single-Photon"[mh]	22
#9	"Tomography X-Ray Computed"[mh]	178
#10	"Single Photon Emission Computed Tomography Computed Tomography"[mh]	3
#11	cat AND ("electron beam" or "electron beams" or examination* or imag* or scan* or x ray*)	6
#12	(comput* AND tomogra*) or CT	292

Searches		
#13	"Magnetic Resonance Imaging"[mh]	277
#14	(magnet* AND resonance) OR mri	417
#15	(magnet* or mr) AND (examination* or imag* or scan* or tomograph* or spectroscop* or multiparametric*)	277
#16	"contrast enhance" or "contrast enhanced" or "contrast enhancing" or contrastenhanc* or ceus or spect or spects or sestamibi* or mibi	53
#17	("contrast enhance" or "contrast enhanced" or "contrast enhancing" or contrastenhanc* or ceus or spect or spects or sestamibi* or mibi) OR ((magnet* or mr) AND (examination* or imag* or scan* or tomograph* or spectroscop* or multiparametric*)) OR ((magnet* AND resonance) OR mri) OR ("Magnetic Resonance Imaging"[mh]) OR ((comput* AND tomogra*) or CT) OR (cat AND ("electron beam" or "electron beams" or examination* or imag* or scan* or x ray*)) OR ("Single Photon Emission Computed Tomography Computed Tomography"[mh]) OR ("Tomography X-Ray Computed"[mh]) OR ("Tomography Emission-Computed Single-Photon"[mh]) OR ("Tomography Emission-Computed"[mh])	823
#18	(("contrast enhance" or "contrast enhanced" or "contrast enhancing" or contrastenhanc* or ceus or spect or spects or sestamibi* or mibi) OR ((magnet* or mr) AND (examination* or imag* or scan* or tomograph* or spectroscop* or multiparametric*)) OR ((magnet* AND resonance) OR mri) OR ("Magnetic Resonance Imaging"[mh]) OR ((comput* AND tomogra*) or CT) OR (cat AND ("electron beam" or "electron beams" or examination* or imag* or scan* or x ray*)) OR ("Single Photon Emission Computed Tomography Computed Tomography"[mh]) OR ("Tomography X-Ray Computed"[mh]) OR ("Tomography Emission-Computed Single-Photon"[mh]) OR ("Tomography Emission-Computed"[mh])) AND (((kidney* AND ("transitional cell" or "transitional cells" or cell or urothelial* or duct or advanc*) AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*))) OR (("renal cell" or "renal cells" or rcc or ccrcc or renal-mass* or "renal tumor" or "renal tumors" or "renal tumours" or "renal tumour" or "grawitz tumor" or "grawitz tumors" or "grawitz tumour" or "grawitz tumours" or hypernephroma* or nephrocarcinoma*)) OR ((("collecting duct" or "collecting ducts") AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*))) OR (((kidney* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*)))) OR ("Kidney Neoplasms"[mhe]))	5

1 **Database name: Medline ALL**

Searches
1 exp *Kidney Neoplasms/ (75501)
2 (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. (16726)

Searches
3 (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. (507)
4 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti,ab. (73655)
5 (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. (877)
6 or/1-5 (111864)
7 *tomography, emission-computed/ or *tomography, emission-computed, single-photon/ or *tomography, x-ray computed/ or *single photon emission computed tomography computed tomography/ (154655)
8 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti,ab. (1327)
9 ((comput* adj3 tomogra*) or (CT not PET)).ti,ab. (665997)
10 exp *Magnetic Resonance Imaging/ (212458)
11 (magnet*-resonance or MRI).ti,ab. (632758)
12 ((magnet* or MR) adj (examination* or imag* or scan* or tomograph* or spectroscop*)).ti,ab. (75805)
13 (contrast-enhanc* or contrastenhanc* or CEUS).ti,ab,kw. (69660)
14 (SPECT or SPECTs or sestamibi* or mibi).ti,ab,kw. (38777)
15 or/7-14 (1313347)
16 6 and 15 (12501)
17 animals/ not humans/ (5237764)
18 16 not 17 (12281)
19 limit 18 to english language (10103)
20 limit 19 to (letter or historical article or comment or editorial or news or case reports) (3796)
21 19 not 20 (6307)
22 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

Searches
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/ (1379258)
23 "organisation for economic co-operation and development"/ (634)
24 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/ (3606459)
25 european union/ (18239)
26 developed countries/ (21655)
27 or/23-26 (3623041)
28 22 not 27 (1287342)
29 21 not 28 (6251)
30 Cost-Benefit Analysis/ (96031)
31 Quality-Adjusted Life Years/ (16997)
32 Markov Chains/ (16539)
33 exp Models, Economic/ (16561)
34 cost*.ti. (153289)
35 (cost* adj2 utilit*).tw. (8371)
36 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (303397)
37 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (51588)
38 (qualit* adj2 adjust* adj2 life*).tw. (19428)
39 QALY*.tw. (15767)
40 (incremental* adj2 cost*).tw. (18869)
41 ICER.tw. (6765)
42 utilities.tw. (10150)
43 markov*.tw. (34270)
44 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (57566)
45 ((utility or effective*) adj2 analys*).tw. (27241)
46 (willing* adj2 pay*).tw. (10970)
47 (EQ5D* or EQ-5D*).tw. (15137)
48 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4434)
49 (european* adj2 quality adj3 ("5" or five)).tw. (805)
50 or/30-49 (541932)
51 (quality adjusted or adjusted life year$).ti,ab,kf. (26626)
52 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (16206)

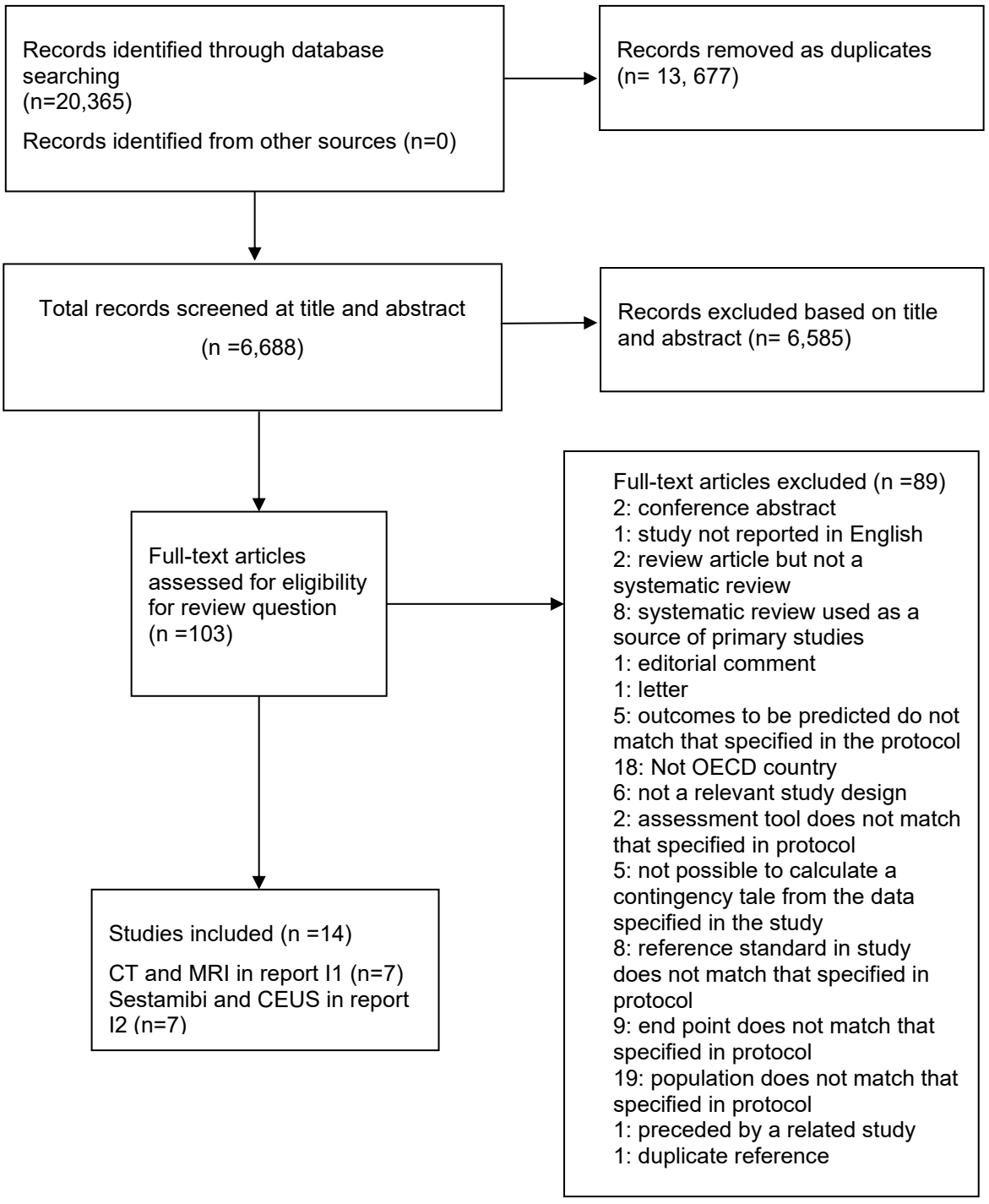
Searches
53 (illness state$1 or health state$1).ti,ab,kf. (9099)
54 (hui or hui1 or hui2 or hui3).ti,ab,kf. (2151)
55 (multiattribute$ or multi attribute$).ti,ab,kf. (1520)
56 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (22311)
57 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (28377)
58 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (2583)
59 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (17100)
60 quality of life/ and ec.fs. (11109)
61 quality of life/ and (health adj3 status).ti,ab,kf. (12729)
62 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ (18189)
63 or/51-62 (115281)
64 Economics/ (27540)
65 Value of life/ (5833)
66 exp "Costs and Cost Analysis"/ (274077)
67 exp Economics, Hospital/ (26015)
68 exp Economics, Medical/ (14450)
69 Economics, Nursing/ (4013)
70 Economics, Pharmaceutical/ (3150)
71 exp "Fees and Charges"/ (31551)
72 exp Budgets/ (14270)
73 budget*.ti,ab. (38428)
74 (economic* or pharmaco?economic*).ti. (65635)
75 (price* or pricing*).ti,ab. (58091)
76 (financ* or fee or fees).ti,ab. (176680)
77 (value adj2 (money or monetary)).ti,ab. (3302)
78 or/64-77 (589850)
79 50 or 63 or 78 (994639)
80 29 and 79 (110)

1

2

Appendix C – Diagnostic evidence study selection

Figure 1: PRISMA diagram for reviews I1 and I2



Appendix D –Diagnostic evidence

Nicolau, 2015

Bibliographic Reference	Nicolau, Carlos; Bunesch, Laura; Pano, Blanca; Salvador, Rafael; Ribal, Maria Jose; Mallofre, Carme; Sebastia, Carmen; Prospective evaluation of CT indeterminate renal masses using US and contrast-enhanced ultrasound.; Abdominal imaging; 2015; vol. 40 (no. 3); 542-51

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • Spain Study dates • Began April 2009 Source of funding • Not reported
Inclusion criteria	Patients with indeterminate renal nodule on a CT
Exclusion criteria	None reported
Number of participants	N=72 (83 lesions in total)
Length of follow-up	For the 50 cysts diagnosed as benign: median, (range); 23 (23–41) months
Loss to follow-up	20 patients were excluded because of a lack of conclusive diagnosis (they did not complete the follow-up or have a histological diagnosis)
Target condition	Solid mass vs cystic lesion
Index test(s)	Contrast-enhanced ultrasound (CEUS)
Index test detail	Interpreted by an experienced nuclear medicine physician

	• Two radiologists with at least 10 years' experience in interpreting CEUS studies independently interpreted the results Qualitative interpretation
Reference standard	Pathological confirmation after surgical intervention Follow-up
Reference standard detail	Histological diagnosis was not obtained for benign cystic lesions. These cysts (n=50) were diagnosed within at least 23 months of follow-up (range 23–41 months) using CEUS ± dedicated CT (computed tomography)/MR (magnetic resonance). 1 lesion was diagnosed and followed with enhanced CT and had disappeared at the 1-year follow-up CT. 32 lesions were diagnosed by histology.
Additional comments	No additional information

Population characteristics

Study-level characteristics

Characteristic	Study (N = 72)
% Female No of events	n = 22 ; % = 31
Age (years (mean, range)) Custom value	64.2 (34-85)
Ethnicity	NR
Tumour / complex cyst size (mm (mean, range)) Custom value	20.7 (5-65)
Location of tumour / complex cyst - Left side No of events	n = 44 ; % = 61
Location of tumour / complex cyst - Right side No of events	n = 39 ; % = 54

Critical appraisal – QUADAS-2

Question	Answer
Risk of Bias	High *[20 patients with 20 nodules were excluded because of a lack of conclusive diagnosis (they did not complete the follow-up or have a histological diagnosis). Lack of information on whether reference standard results were interpreted with knowledge of index test results. No information on timing between index text and reference test and potential risk of bias associated with follow-up time used as the reference standard.]*
Directness	Partially applicable *(Results reported are combined for baseline US + CEUS so the results are not for solely CEUS which is the index test specified in the protocol for the review question. It is unclear if combining the result had an impact on sensitivity and specificity.)*

Parihar, 2023

Bibliographic Reference	Parihar, Ashwin Singh; Mhlanga, Joyce; Ronstrom, Carrie; Schmidt, Lisa R; Figenshau, Robert S; Dehdashti, Farrokh; Wahl, Richard L; Diagnostic Accuracy of 99mTc-Sestamibi SPECT/CT for Characterization of Solid Renal Masses.; Journal of nuclear medicine : official publication, Society of Nuclear Medicine; 2023; vol. 64 (no. 1); 90-95

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • US Study dates • September 2018 - October 2021 Sources of funding • Not reported
Inclusion criteria	Previous tests • Prior contrast enhanced CT was conducted in 20 patients Patients with an indeterminant solid renal lesions

Exclusion criteria	Participants with no histopathological confirmation
Number of participants	^{99m}Tc-sestamibi SPECT/CT was performed in 42 participants but only 27 had histopathological confirmation and were included in the analysis (36 renal masses in total were included)
Length of follow-up	Not reported
Loss to follow-up	Not reported
Target condition	Malignant diagnosis vs benign diagnosis
Index test(s)	^{99m}Tc-sestamibi SPECT/CT
Index test detail	Interpreted by an experienced nuclear medicine physician Qualitative and quantitative interpretation
Reference standard	Pathological confirmation from biopsy / surgery
Reference standard detail	Final histopathologic diagnosis by either surgery (n=23) or biopsy (n=4)
Additional comments	No additional information

Population characteristics

Study-level characteristics

Characteristic	Study (N = 27)
% Female No of events	n = 9 ; % = 33
Age Median (IQR)	68 (58.5 to 77)
Ethnicity	NR
Tumour / complex cyst size (cm) Median (IQR)	3.3 (2.07 to 4.57)
Location of tumour / complex cyst - Tumour laterality Left side	n = 19; % = 52.8

Characteristic	Study (N = 27)
No of events	
Location of tumour / complex cyst - Tumour laterality Right side No of events	n = 17; % = 47.2

Critical appraisal - QUADAS-2

Question	Answer
Risk of Bias	High *(Unclear if consecutive patients were selected and patients with no histopathologic determination were excluded from study. The interpreting physician was aware of the clinical information and the other imaging findings.)*
Directness	Directly applicable

Sheikhbahaei, 2017

Bibliographic Reference	Sheikhbahaei, Sara; Jones, Christopher S; Porter, Kristin K; Rowe, Steven P; Gorin, Michael A; Baras, Alex S; Pierorazio, Phillip M; Ball, Mark W; Higuchi, Takahiro; Johnson, Pamela T; Solnes, Lilja B; Epstein, Jonathan I; Allaf, Mohamad E; Javadi, Mehrbod S; Defining the Added Value of 99mTc-MIBI SPECT/CT to Conventional Cross-Sectional Imaging in the Characterization of Enhancing Solid Renal Masses.; Clinical nuclear medicine; 2017; vol. 42 (no. 4); e188-e193

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • US Study dates • 2014 - 2015 Sources of funding

	• This study was funded by Buerger Family Scholar Fund and the National Kidney Foundation of Maryland (Philanthropic funds). The authors had no conflicts of interest to disclose
Inclusion criteria	Previous tests • Conventional imaging was performed within 8 weeks before 99mTc-MIBI SPECT/CT as CT in 35 patients, contrast-enhanced MRI in 12 patients, and non–contrast-enhanced MRI in 1. Solitary solid enhancing T1 renal mass
Exclusion criteria	Participants with no histopathological confirmation Younger than 18 years Pregnant Diagnosed with other malignancies Evidence of nodal or distant metastasis
Number of participants	N=48
Length of follow-up	Not reported
Loss to follow-up	Not reported
Target condition	Malignant diagnosis vs benign diagnosis
Index test(s)	^{99m}Tc-sestamibi SPECT/CT
Index test detail	Interpreted by an experienced nuclear medicine physician • Interpreted independently by 2 nuclear medicine fellowship-trained radiologists who were blinded to patient outcomes Qualitative interpretation
Reference standard	Pathological confirmation after surgical intervention
Reference standard detail	Surgery for either partial or radical nephrectomy.

Population characteristics

Study-level characteristics

Characteristic	Study (N = 48)
% Female No of events	n = 13 ; % = 27
Age (years) Median (IQR)	59 (NR to NR)
Ethnicity	NR

Critical appraisal - QUADAS-2

Question	Answer
Risk of Bias	Moderate *(Lack of information on patient enrolment and if it was consecutive or random)*
Directness	Directly applicable

Sistani, 2021

Bibliographic Reference	Sistani, Golmehr; Bjazevic, Jennifer; Kassam, Zahra; Romsa, Jonathan; Pautler, Stephen; The value of 99mTc-sestamibi single-photon emission computed tomography-computed tomography in the evaluation and risk stratification of renal masses.; Canadian Urological Association journal = Journal de l'Association des urologues du Canada; 2021; vol. 15 (no. 6); 197-201

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • Canada Study dates • December 2018 - March 2020 Sources of funding

	• Ontario Health Insurance Plan
Inclusion criteria	Previous tests • CT scan Patients with an indeterminant solid renal lesions
Exclusion criteria	Participants with no histopathological confirmation
Number of participants	N=29 (with a total of 31 lesions)
Length of follow-up	Not reported
Loss to follow-up	Not reported
Target condition	Malignant diagnosis vs benign diagnosis
Index test(s)	^{99m}Tc-sestamibi SPECT/CT
Index test detail	Interpreted by an experienced nuclear medicine physician All MIBI SPECT-CT images were reviewed independently by an experienced nuclear medicine specialist and a dual radiology/nuclear medicine resident. A final diagnostic interpretation was made by consensus. There was no information about time interval between index test and reference standard . Qualitative interpretation
Reference standard	Pathological confirmation from biopsy / surgery
Reference standard detail	Image-guided percutaneous biopsy or surgical excision with partial or radical nephrectomy

Population characteristics

Study-level characteristics

Characteristic	Study (N = 29)
% Female No of events	n = 6 ; % = 20.7
Age (years)	59.9 (NR to NR)

Characteristic	Study (N = 29)
Median (IQR)	
Ethnicity	NR
Tumour / complex cyst size - > 4 cm No of events	n = 5 ; % = 16.1
Tumour / complex cyst size - <4 cm No of events	n = 26 ; % = 83.9
Complexity of tumour / complex cyst - Solid enhancing mass No of events	n = 26 ; % = 83.9
Complexity of tumour / complex cyst - Bosniak 4 cyst No of events	n = 5 ; % = 16.1

Critical appraisal - QUADAS-2

Question	Answer
Risk of Bias	High *(Does not state that consecutive patients were enrolled or that it was a random sample. No information reported on intervals, only that the study was retrospective. The physician interpreting the images was not blinded to patient records.)*
Directness	Directly applicable

Tzortzakakis, 2022

Bibliographic Reference	Tzortzakakis, A.; Papathomas, T.; Gustafsson, O.; Gabrielson, S.; Trpkov, K.; Ekstrom-Ehn, L.; Arvanitis, A.; Holstensson, M.; Karlsson, M.; Kokaraki, G.; Axelsson, R.; 99mTc-Sestamibi SPECT/CT and histopathological features of oncocytic renal neoplasia; Scandinavian Journal of Urology; 2022; vol. 56 (no. 56); 375-382

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • Sweden

	Study dates • September 2015 - September 2019 Sources of funding • Supported by Sweden's innovation agency VINNOVA as part of the Molecular Imaging for Differentiation of Oncocytomas from Renal cancer (MIDOR)
Inclusion criteria	T1 renal tumours Patients with an indeterminant solid renal lesions
Exclusion criteria	Evidence of nodal or distant metastasis T2+ tumours, tumours >7 cm in maximum diameter
Number of participants	N=57
Length of follow-up	Not reported
Loss to follow-up	Not reported
Target condition	Malignant diagnosis vs benign diagnosis
Index test(s)	^{99m}Tc-sestamibi SPECT/CT
Index test detail	Interpreted by an experienced nuclear medicine physician Two readers independently and simultaneously performed the visual evaluation: a Consultant in Radiology and Nuclear Medicine and a Consultant in Radiology. Qualitative and quantitative interpretation
Reference standard	Pathological confirmation from biopsy / surgery
Reference standard detail	The confirmed histopathological diagnoses and/or updated diagnoses, based on consensus, were used as the gold standard to correlate with the results from 99mTc-Sestamibi SPECT/CT examinations.

Population characteristics

Study-level characteristics

Characteristic	Study (N = 52)
% Female No of events	n = 19 ; % = 33
Age (years) Median (IQR)	68 (60 to 76)
Ethnicity	NR
Tumour / complex cyst size (mm) Median (IQR)	24 (17 to 39)

Critical appraisal - QUADAS-2

Question	Answer
Risk of Bias	Moderate *(States that the study was non-randomised but not clear whether or not patients were enrolled consecutively. Lack of information on time interval between the index test and reference test. Lack of information in interpreting physician's knowledge of histopathology results.)*
Directness	Directly applicable

Viswambaram, 2022

Bibliographic Reference	Viswambaram, Pravin; Swarbrick, Nicole; Picardo, Alarick; Hohnen, Andrew; Pham, Kevin; Macdonald, William; Hayne, Dickon; Hamid, Akhlil; Technetium-99 m-sestamibi single-photon emission computerised tomography (CT)/CT in the prediction of malignant versus benign small renal masses.; BJU international; 2022; vol. 130suppl3; 23-31

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • Australia

	Study dates • June 2018 - October 2020 Sources of funding • Not reported (authors sated they had no conflicts of interest to declare)
Inclusion criteria	Age >18 years Patients with an indeterminant solid renal lesions
Exclusion criteria	Younger than 18 years Small tumours (<2 cm diameter), unless exophytic, and cystic tumours.
Number of participants	N=74
Length of follow-up	Not reported
Loss to follow-up	Not reported
Target condition	Malignant diagnosis vs benign diagnosis
Index test(s)	^{99m}Tc-sestamibi SPECT/CT
Index test detail	Interpreted by an experienced nuclear medicine physician • Interpretation by 2 nuclear medicine physicians Qualitative and quantitative interpretation
Reference standard	Pathological confirmation from biopsy / surgery
Reference standard detail	Core renal mass biopsy, 34 (45.9%); Surgery, 40 (54.1%)
Additional comments	No additional information

Population characteristics

Study-level characteristics

Characteristic	Study (N = 74)
% Female No of events	n = 23 ; % = 31.1
Age (years) Median (IQR)	66 (28 to 84)
Ethnicity	NR
Tumour / complex cyst size (mm (median and range)) Custom value	34 (17-70)
Location of tumour right side No of events	n = 41 ; % = 55
Location of tumour / complex cyst - Location of tumour Left side No of events	n = 33 ; % = 45

Critical appraisal - QUADAS-2

Question	Answer
Risk of Bias	Moderate *(No mention of random sampling and lack of clarity on whether consecutive patients were enrolled. Lack of information on time interval between index test and reference standard. No information on knowledge of index test results when interpreting reference standard.)*
Directness	Directly applicable

Yong, 2024

Bibliographic Reference	Yong, Courtney; Tong, Yan; Tann, Mark; Sundaram, Chandru P; The impact of sestamibi scan on clinical decision-making for renal masses: An observational single-center study.; Indian journal of urology : IJU : journal of the Urological Society of India; 2024; vol. 40 (no. 3); 151-155

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • US Study dates • 2008 - 2022 Sources of funding • Financial support and sponsorship reported as nil
Inclusion criteria	Selected based on physician judgment
Exclusion criteria	Sestamibi scan was performed for indications other than evaluation of a renal mass
Number of participants	N=43
Length of follow-up	Median (range): 19 (2 -163) months
Loss to follow-up	Not reported
Target condition	Malignant diagnosis vs benign diagnosis
Index test(s)	^{99m}Tc-sestamibi SPECT/CT
Index test detail	Interpreted by an experienced nuclear medicine physician • Initial clinical radiological read was conducted by 7 separate nuclear medicine specialists. Images were re-reviewed by an experienced nuclear medicine radiologist with 20 years of experience. Qualitative and quantitative interpretation
Reference standard	Pathological confirmation from biopsy / surgery
Reference standard detail	Surgery (63%) and biopsy (42%)
Additional comments	No additional information.

Population characteristics

Study-level characteristics

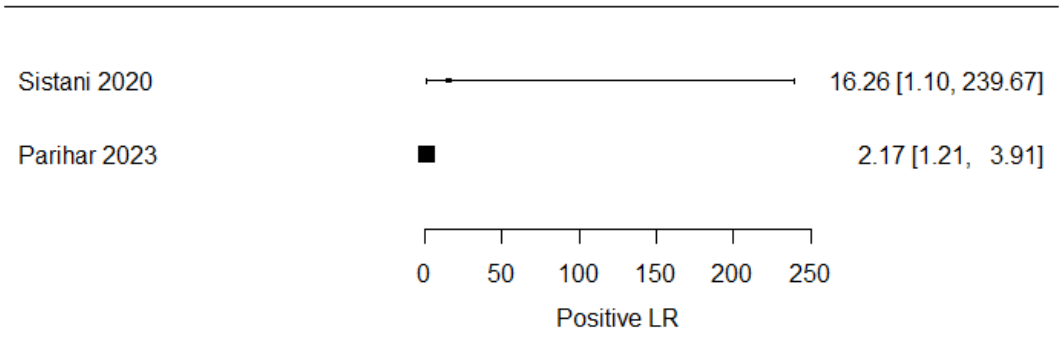
Characteristic	Study (N = 43)
% Female No of events	n = 11 ; % = 26
Age (years) Mean (SD)	63 (NR)
Ethnicity	NR
Tumour / complex cyst size - Tumour size (cm) Mean (SD)	4 (1.8)
Renal function - Creatinine at diagnosis Mean (SD)	1 (0.28)
Renal function - Creatinine at last follow-up Mean (SD)	1.2 (0.39)

Critical appraisal – QUADAS-2

Question	Answer
Risk of Bias	Moderate *(Unclear if patients were selected randomly or consecutively. Unclear if those interpreting reference standard results had knowledge of the index test results or not. Lack of clarity on interval between index test and reference standard.)*
Directness	Directly applicable

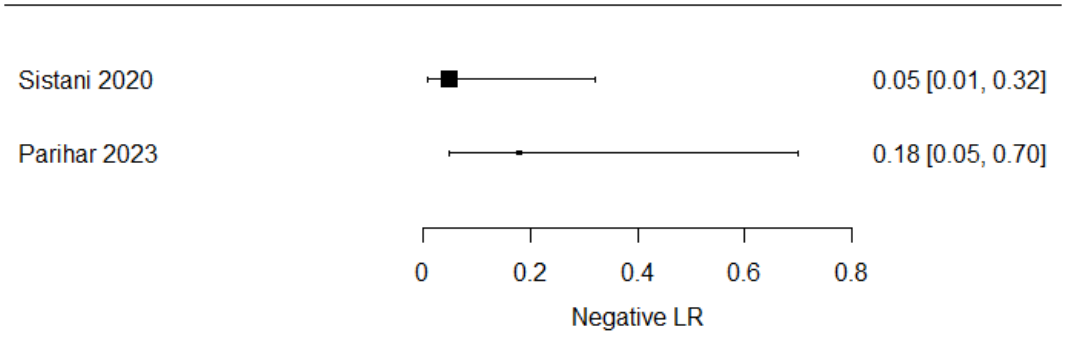
Appendix E – Forest plots

Figure 2: Forest plot for positive likelihood ratio of ^{99m}Tc-sestamibi SPECT/CT (lesions)



LR: likelihood ratio

Figure 3: Forest plot for negative likelihood ratio of ^{99m}Tc-sestamibi SPECT/CT (lesions)



LR: likelihood ratio

Figure 4: Forest plot for ^{99m}Tc-sestamibi SPECT/CT sensitivity and specificity (lesions)

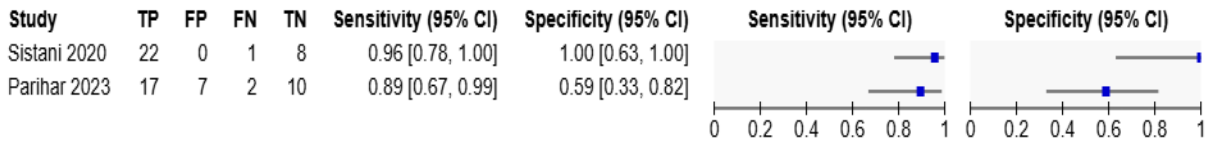
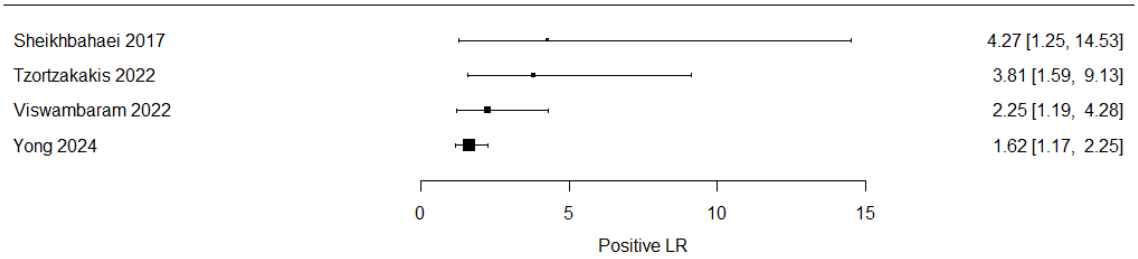
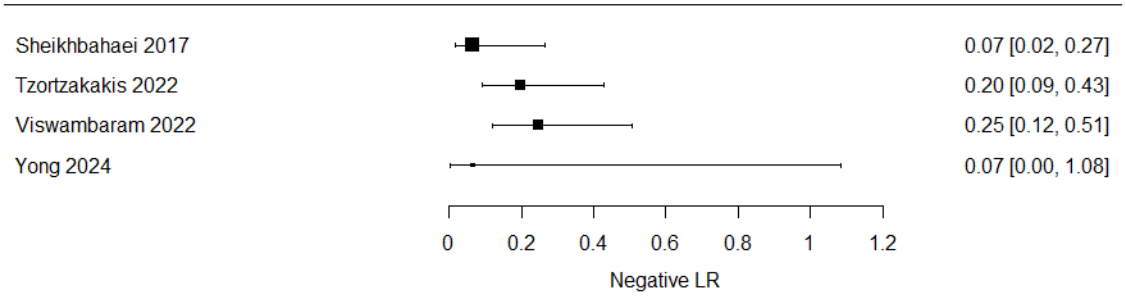


Figure 5: Forest plot for positive likelihood ratio of ^{99m}Tc-sestamibi SPECT/CT (person)



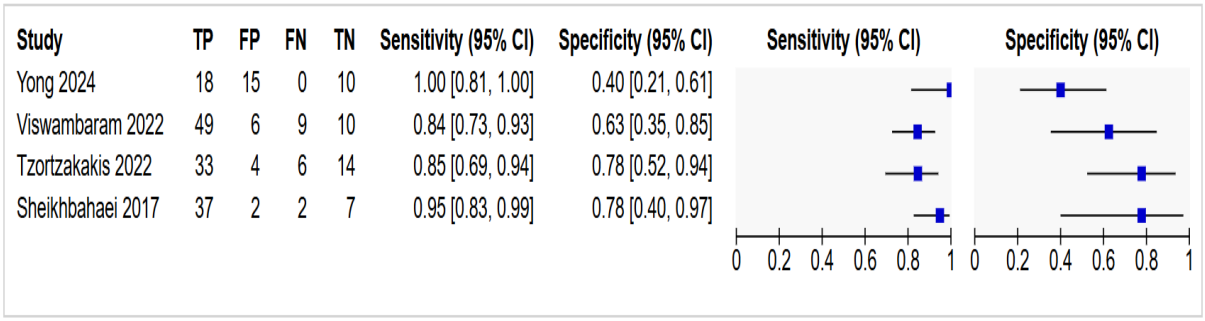
LR: likelihood ratio

Figure 6: Forest plot for negative likelihood ratio of ^{99m}Tc-sestamibi SPECT/CT (persons)



LR: likelihood ratio

Figure 7: Forest plot for ^{99m}Tc-sestamibi SPECT/CT sensitivity and specificity (persons)



Appendix F – GRADE tables

Likelihood ratios were chosen as the primary measure of interest for decision making and assessment of inconsistency and imprecision were based on these data. Clinical decision thresholds were chosen as 2 for LR+ and 0.5 for LR- and the line of no effect (being 1.0) as the second clinical decision line in both cases.

^{99m}Tc-sestamibi SPECT/CT

Table 11: Clinical evidence profile (diagnostic accuracy) for ^{99m}Tc-sestamibi SPECT/CT (lesions as unit of analysis)

No of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Effect estimate range	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Sistani 2020)	Retrospective cohort	29 (31 lesions)	0.96 (0.79, 0.99)	1.00 (0.68, 1.00)	LR + 16.26 (1.10, 239.67) LR – 0.05 (0.01, 0.32)	LR + 2.17 – 16.26 LR – 0.05 – 0.18	Very serious[1] for LR + Very serious[1] for LR -	Very Serious[2] for LR + Serious[3] for LR -	Not serious for LR+ Not serious for LR-	Very Serious[4] for LR + Serious[5] for LR -	VERY LOW for LR + VERY LOW for LR -
1 (Parihar 2023)	Retrospective cohort	27 (36 lesions)	0.89 (0.69, 0.97)	0.59 (0.36, 0.78)	LR + 2.17 (1.21, 3.91)						

					LR – 0.18 (0.05, 0.70)						

1. Downgraded twice for risk of bias. Both studies had high risk of bias as assessed by QUADAS-2
2. Downgraded twice for inconsistency. Very serious inconsistency on visual inspection of point estimates and confidence intervals
3. Downgraded once for inconsistency. Serious inconsistency on visual inspection of point estimates and confidence intervals
4. Downgraded once for imprecision. ≥50% studies have 95% CI that crosses 1 decision making thresholds (for LR+: 1 ≤ LR <2)
5. Downgraded once for imprecision. ≥50% studies has a 95% CI that crosses 1 decision making thresholds (for LR-: 0.5 ≤ LR <1)

Table 12: Clinical evidence profile (diagnostic accuracy) for 99mTc-sestamibi SPECT/CT (person as unit of analysis)

No of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Effect estimate range	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Sheikhbahaei 2017)	Retrospective cohort	48	94.9 (83.1, 98.6)	77.8 (45.3, 93.7)	LR + 4.27 (1.25, 14.53) LR – 0.07 (0.02, 0.27)	LR + 2.17 – 16.26 LR – 0.05 – 0.18	Serious[1] for LR + Serious[1] for LR -	Serious[2] for LR + Very serious[3] for LR -	Not serious for LR + Not serious for LR -	Serious[4] for LR+ Not serious for LR-	VERY LOW for LR+ VERY LOW for LR -

1 (Tzortzakakis 2022)	Prospective cohort	57	84.6 (70.3, 92.8)	77.8 (54.8, 91.0)	LR + 3.81 (1.59, 9.13) LR – 0.20 (0.09, 0.43)						
1 (Viswambaram 2022)	Prospective cohort	74	84.5 (73.1, 91.6)	62.5 (38.6, 81.5)	LR + 2.25 (1.19, 4.28) LR – 0.25 (0.12, 0.51)						
1 (Yong 2024)	Retrospective cohort	43	97.3 (78.6, 99.7)	40.0 (23.4, 59.3)	LR + 1.62 (1.17, 2.25) LR - 0.07 (0.00, 1.08)						

1. Downgraded once for risk of bias. ≥50% of studies had some concerns or high risk of bias as assessed by QUADAS-2
2. Downgraded once for risk of bias. Serious inconsistency on visual inspection of point estimates and confidence intervals
3. Downgraded twice for inconsistency. Very serious inconsistency on visual inspection of point estimates and confidence intervals
4. Downgraded once for imprecision. ≥50% of studies had 95% CI which crosses 1 decision making thresholds (for LR+: 1 ≤ LR <2)

CEUS

Table 13: Clinical evidence profile (diagnostic accuracy) for CEUS (lesions as unit of analysis)

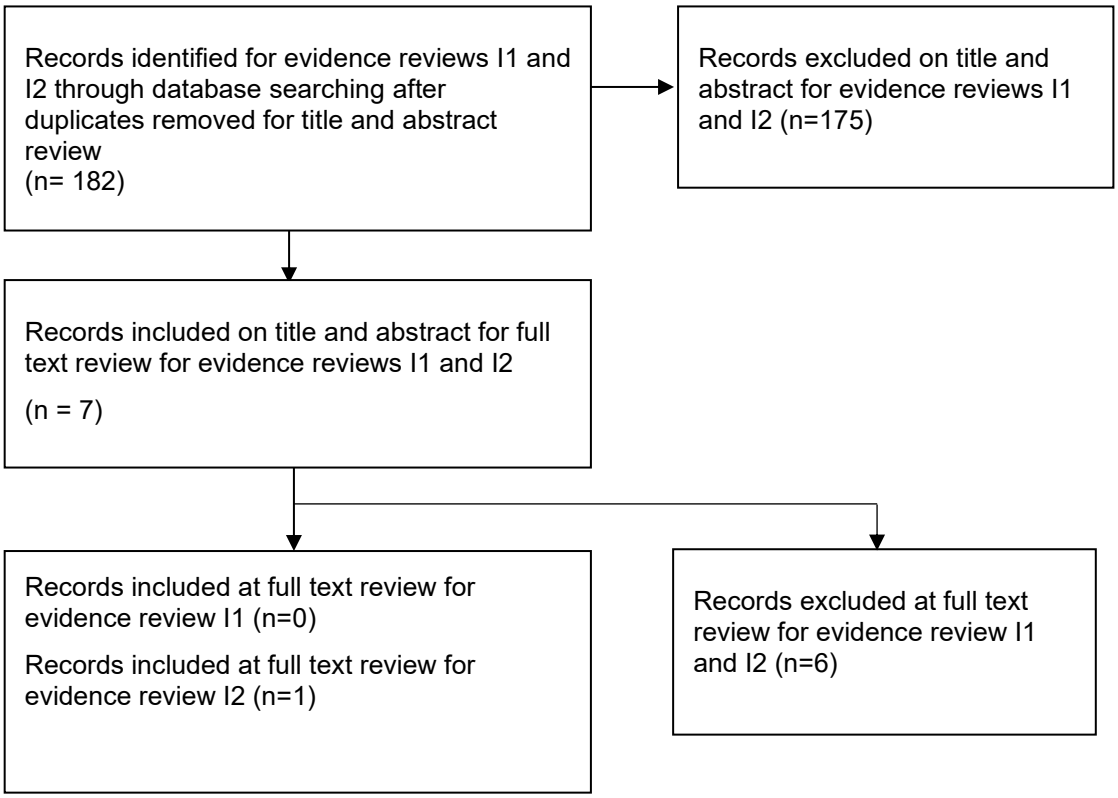
No of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
1 (Nicolau 2015)	Prospective cohort	72 (83 lesions)	0.94 (0.80, 0.99)	0.96 (0.86, 1.00)	LR + 23.49 (6.02, 91.56)	Very serious[1]	Serious[2]	Not serious	Not serious	VERY LOW
					LR – 0.06 (0.02, 0.24)	Very serious[1]	Serious[2]	Not serious	Not serious	VERY LOW

CI: confidence interval; LR: likelihood ratio

1. Downgraded twice for risk of bias. ≥50% of the weighting of studies had high risk of bias as assessed by QUADAS-2
2. Downgraded once for inconsistency. Serious inconsistency rating due to single study data

Appendix G – Economic evidence study selection

Figure 8: Economic evidence study selection



Appendix H – Economic evidence tables

Table 14: Economic evidence table

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Spiesecke et al. (2021) Germany Cost-utility analysis	Diagnosis and monitoring with • contrast-enhanced CT (CECT) • contrast-enhanced MRI (CEMRI) • contrast-enhanced ultrasound (CEUS)	Population: adults with Bosniak 2F or 3 renal cysts. Decision tree followed by Markov, separated into outcomes of malignant or benign lesions. Source of efficacy & resource use data: Meta-analysis and literature search Source of unit costs: Hospital finance department for imaging costs, surgical costs and inpatient care. Purchase prices for contrast agents.	Costs: imaging, surgical treatment and inpatient care Outcomes: quality of life in different tumour health states (without tumour, with metastatic tumour, with localised tumour, death) Results: Bosniak 2F CECT: total cost €1600 (£1,496), total QALYs 8.0868 CEMRI: total cost €1632 (£1,526), total QALYs 8.0872 CEUS: total cost €1511 (£1,413), total QALYs 8.0878 Bosniak 3 CECT: total cost €4499 (£4,207), total QALYs 8.0245 CEMRI: total cost €5174 (£4,838), total QALYs 8.0282 CEUS: total cost €4256 (£3,980), total QALYs 8.0328	Compared with CECT and CEMRI, CEUS is dominant for both Bosniak 2F and 3.	Perspective: German healthcare system Currency: € Cost year: 2018 Time horizon: 10 years Discounting: 3% Applicability: partially applicable – German hospital perspective and only a very specific subgroup of the population. Quality: minor limitations

Table 15: Applicability and quality checklist for economic evaluations – Spiesecke et al. 2021

Study ID: Spiesecke (2021) Cost-effectiveness analysis of multiple imaging modalities in diagnosis and follow-up of intermediate complex cystic renal lesions		
Section 1: Applicability	**Rating**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	These include ceMRI, ceCT, CEUS
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	German hospital setting
1.4 Is the perspective for costs appropriate for the review question?	Partly	Hospital cost perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Discount rate of 3%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	Utility values taken from the literature which were originally derived using the EQ-5D-5L and the Dutch tariff.
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	

Section 2: Study limitations	Rating	
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	Decision tree on diagnosis followed by outcomes of true/false positives/negatives.
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	10-year time horizon captures the duration of suggested follow-up; however, patients enter the model aged 60, and the consequences of misdiagnosis could have effects after this time horizon.
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	Meta-analysis of diagnostic accuracy, includes all applicable sources
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	Includes detailed costing analysis for imaging (e.g. consultation, contrast agent, computer-aided image processing), cost of surgical treatment
2.7 Are the estimates of resource use from the best available source?	Partially	From a single German hospital's financial department.
2.8 Are the unit costs of resources from the best available source?	Partially	From a single German hospital's financial department.
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	No	No conflicts of interest
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Appendix I – Health economic model

No original economic modelling was conducted for this review question.

Appendix J – Excluded studies

Diagnostic accuracy references excluded at full text (n = 89)

Table 16: Excluded diagnostic accuracy studies

Study	Reason
Almalki, Yassir Edrees, Basha, Mohammad Abd Alkhalik, Refaat, Rania et al. (2023) Bosniak classification version 2019: a prospective comparison of CT and MRI. European radiology 33(2): 1286-1296	- Not OECD country *Egypt*
Almeida Dores, J., Kronenberg, P., Bargao Santos, P. et al. (2016) Renal oncocytoma: Is URO-CT useful in histological diagnosis?. Acta Urologica Portuguesa 33(3): 98-103	- Study not reported in English
Atri, Mostafa, Tabatabaeifar, Leila, Jang, Hyun-Jung et al. (2015) Accuracy of Contrast-enhanced US for Differentiating Benign from Malignant Solid Small Renal Masses. Radiology 276(3): 900-8	- Population *Different target condition to protocol criteria - this study is looking to investigate people with malignant mass v benign mass*
Balyemez, Fikret, Aslan, Ahmet, Inan, Ibrahim et al. (2017) Diffusion-weighted magnetic resonance imaging in cystic renal masses. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 11(12): e8-e14	- End point do not match that specified in the protocol *Study outcome was on ADC values and sensitivity and specificity were reported for a cut off ADC value. The study aim was to characterise complex renal cystic masses, therefore only cystic masses were included. Also, the reference test was not consistent for all participants and include histopathological results and follow-up*
Barr, Richard G (2022) Use of lumason/sonovue in contrast-enhanced ultrasound of the kidney for characterization of renal masses-a meta-analysis. Abdominal radiology (New York) 47(1): 272-287	- Systematic review used as source of primary studies
Barr, Richard G; Peterson, Cynthia; Hindi, Ammar (2014) Evaluation of indeterminate renal masses with contrast-enhanced US: a diagnostic performance study. Radiology 271(1): 133-42	- Population *Not investigating a population with condition of interest - looking at CEUS to identify benign/malignant rather than solid renal mass vs. cystic mass.*
Bertolotto, Michele, Cicero, Calogero, Perrone, Rosaria et al. (2015) Renal Masses With Equivocal Enhancement at CT: Characterization With Contrast-	- Population *Mainly used to differentiate between malignant and benign*

Study	Reason
Enhanced Ultrasound. AJR. American journal of roentgenology 204(5): w557-65	
Catalano, C, Fraioli, F, Laghi, A et al. (2003) High-resolution multidetector CT in the preoperative evaluation of patients with renal cell carcinoma. AJR. American journal of roentgenology 180(5): 1271-7	- Not possible to calculate a contingency table from the data specified in the protocol *End point was level of agreement between image assessment and pathologic findings but sensitivity and specificity were only reported for a subgroup of the population (evaluating stage 1 of RCC for fat infiltration). No other data for contingency table reported.*
Chen, Lin, Wang, Ling, Diao, Xuehong et al. (2015) The diagnostic value of contrast-enhanced ultrasound in differentiating small renal carcinoma and angiomyolipoma. Bioscience trends 9(4): 252-8	- Population *Aims to look at diagnostic value of differentiating between small renal carcinoma and angiomyolipoma only.*
Das, Chandan J, Agarwal, Keshav, Sharma, Sanjay et al. (2023) Role of Contrast-Enhanced Ultrasound in Evaluation of Cystic Renal Mass. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 42(12): 2873-2881	- Not a relevant study design *Long follow-up (3 years) and pathological confirmation not available for all patients. Study comparing CEUS to CECT. CEUS used to differentiate between benign and malignant.*
de Silva, Suresh, Lockhart, Kathleen Rebecca, Aslan, Peter et al. (2021) The diagnostic utility of diffusion weighted MRI imaging and ADC ratio to distinguish benign from malignant renal masses: sorting the kittens from the tigers. BMC urology 21(1): 67	- Outcome to be predicted do not match that specified in the protocol *Study reported on ADC values of various types of renal masses*
Deb, Abdalla Ali, Agag, Ayman, Naushad, Naufal et al. (2022) The value of sestamibi single-photon emission computed tomography/computed tomography in differentiating and staging renal cell carcinomas: A systematic review. Current urology 16(1): 32-37	- Systematic review used as source of primary studies
Eisenbrey, John R, Shaw, Colette M, Lyshchik, Andrej et al. (2015) Contrast-Enhanced Subharmonic and Harmonic Ultrasound of Renal Masses Undergoing Percutaneous Cryoablation. Academic radiology 22(7): 820-6	- Population *Looking at population receiving cryoablation only and CEUS used to differentiate between benign and malignant*
Elbanna, Khaled Y, Jang, Hyun-Jung, Kim, Tae Kyoung et al. (2021) The added value of contrast-enhanced ultrasound in	- Population *A significant proportion of patients did not have CT/MRI prior to CEUS.*

Study	Reason
evaluation of indeterminate small solid renal masses and risk stratification of cystic renal lesions. European radiology 31(11): 8468-8477	
Fang, Liang, Bai, Kun, Chen, Yue et al. (2021) A comparative study of contrast-enhanced ultrasound and contrast-enhanced CT for the detection and characterization of renal masses. Bioscience trends 15(1): 24-32	- Not OECD country *China*
Ferda, Jiri, Hora, Milan, Hes, Ondrej et al. (2007) Computed tomography of renal cell carcinoma in patients with terminal renal impairment. European journal of radiology 63(2): 295-301	- Outcome to be predicted do not match that specified in the protocol *Study does not report on any diagnostic accuracy outcomes (sensitivity, specificity, PPV, NPV or likelihood ratios) or clinical outcomes specified in the protocol.*
Furrer, Marc A, Spycher, Samuel C J, Buttiker, Sophia M et al. (2020) Comparison of the Diagnostic Performance of Contrast-enhanced Ultrasound with That of Contrast-enhanced Computed Tomography and Contrast-enhanced Magnetic Resonance Imaging in the Evaluation of Renal Masses: A Systematic Review and Meta-analysis. European urology oncology 3(4): 464-473	- Systematic review used as source of primary studies
Gobara, Aiko, Yoshizako, Takeshi, Yoshida, Rika et al. (2019) T1a renal cell carcinoma on unenhanced CT: analysis of detectability and imaging features. Acta radiologica open 8(5): 2058460119849706	- Reference standard in study does not match that specified in protocol *Refence standard include pathology and contrast-enhanced CT and unable to tell if both were used or either*
Goyal, Ankur, Sharma, Raju, Bhalla, Ashu S et al. (2018) Comparison of MDCT, MRI and MRI with diffusion-weighted imaging in evaluation of focal renal lesions: The defender, challenger, and winner!. The Indian journal of radiology & imaging 28(1): 27-36	- Not OECD country *India*
Grajo, Joseph R, Terry, Russell S, Ruoss, Justin et al. (2019) Using Aorta-Lesion-Attenuation Difference on Preoperative Contrast-enhanced Computed Tomography Scan to Differentiate Between Malignant and Benign Renal Tumors. Urology 125: 123-130	- Assessment tool do not match that specified in the protocol *Study used quantitative method of assessing CT - aorta-lesion-attenuation difference (ALAD)*
Hashimoto, Masahiro, Ohkuma, Kiyoshi, Akita, Hirotaka et al. (2019) Usefulness of	- End point do not match that specified in the protocol

Study	Reason
contrast-enhanced ultrasonography for diagnosis of renal cell carcinoma in dialysis patients: Comparison with computed tomography. Medicine 98(47): e18053	*Only includes participants with solid renal masses - target condition is not solid vs cystic.*
Ho, V.B. and Choyke, P.L. (2004) MR evaluation of solid renal masses. Magnetic Resonance Imaging Clinics of North America 12(3): 413-427	- Review article but not a systematic review
Homayounieh, Fatemeh, Gopal, Nikhil, Firouzabadi, Fatemeh Dehghani et al. (2024) A Prospective Study of the Diagnostic Performance of Photon-Counting CT Compared With MRI in the Characterization of Renal Masses. Investigative radiology	- Not possible to calculate a contingency table from the data specified in the protocol *Study did not report sensitivity, specificity, PPV or NPV. Study focused on comparing the findings on proton-counting CT with those on MRI by 2 radiologists.*
Hovsepian, D M, Levy, H, Amis, E S Jr et al. (1990) MR evaluation of renal space-occupying lesions: diagnostic criteria. Urologic radiology 12(2): 74-9	- End point do not match that specified in the protocol *Study identified and defined MR imaging criteria that can be used in diagnosis/classification of renal lesions. Sensitivity and specificity not reported. Also, reference test included pathology and well-established US and/or CT criteria*
Jin, Dong-Dong, Zhuang, Bo-Wen, Lin, Ke et al. (2024) Contrast-enhanced US Bosniak Classification: intra- and inter-rater agreement, confounding features, and diagnostic performance. Insights into imaging 15(1): 285	- Not OECD country *China*
Jin, Li and Xie, Feng (2020) Untargeted Contrast-Enhanced Ultrasound Versus Contrast-Enhanced Computed Tomography: A Differential Diagnostic Performance (DDP) Study for Kidney Lesions. Clinics (Sao Paulo, Brazil) 75: e1489	- Not OECD country *China*
Kambadakone, Avinash, Arasu, Vignesh A, Samir, Anthony E et al. (2012) Qualitative assessment of enhancement in a renal mass: contribution of subtraction CT. Journal of computer assisted tomography 36(4): 381-7	- Reference standard in study does not match that specified in protocol *Reference standard included biopsy, surgery and follow-up, with the majority receiving follow-up. Number of patients that had biopsy and or surgery were specified but were not separated in the final analysis for diagnostic outcomes.*
Kang, Stella K, Zhang, Angela, Pandharipande, Pari V et al. (2015) DWI for	- Systematic review used as source of primary studies

Study	Reason
Renal Mass Characterization: Systematic Review and Meta-Analysis of Diagnostic Test Performance. AJR. American journal of roentgenology 205(2): 317-24	
Kim, Jae Heon, Sun, Hwa Yeon, Hwang, Jiyoung et al. (2016) Diagnostic accuracy of contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging of small renal masses in real practice: sensitivity and specificity according to subjective radiologic interpretation. World journal of surgical oncology 14(1): 260	- Population *Some participants were excluded for refusing surgery. Also, scanners used on index test used a 5-point scale rated from 1- definitely not cancer to 5- definitely cancer, but the analysis only included categories 3 to 5. Unable to obtain 2x2 table for whole population*
Kim, Sooah, Jain, Monica, Harris, Andrew B et al. (2009) T1 hyperintense renal lesions: characterization with diffusion-weighted MR imaging versus contrast-enhanced MR imaging. Radiology 251(3): 796-807	- Conference abstract
Kreft, B P, Muller-Miny, H, Sommer, T et al. (1997) Diagnostic value of MR imaging in comparison to CT in the detection and differential diagnosis of renal masses: ROC analysis. European radiology 7(4): 542-7	- Reference standard in study does not match that specified in protocol *Reference standard included histology, and follow-up or angiography*
Kwon, Taekmin, Jeong, In Gab, Yoo, Sangjun et al. (2015) Role of MRI in indeterminate renal mass: diagnostic accuracy and impact on clinical decision making. International urology and nephrology 47(4): 585-93	- Reference standard in study does not match that specified in protocol *Reference standard included pathology for 74.2% of population and 18-month follow-up for 25.8%*
Laguna, M.P. (2016) Re: Prospective Evaluation of 99mTc-Sestamibi SPECT/CT for the Diagnosis of Renal Oncocytomas and Hybrid Oncocytic/Chromophobe Tumors. Journal of Urology 195(6): 1718-1719	- Editorial comment
Lal, N.R., Boruah, D.K., Raj, G. et al. (2024) Role of Advanced Magnetic Resonance Imaging (MRI) in the Evaluation of Renal Masses: A Prospective Cross-Sectional Study. International Journal of Pharmaceutical and Clinical Research 16(6): 2230-2236	- Not OECD country *India*
Li, Guorong, Cuilleron, Muriel, Gentil-Perret, Anne et al. (2004) Characteristics of image-detected solid renal masses: implication for optimal treatment. International journal of	- Population *Population excludes people with cystic masses. Also, diagnostic outcomes as per protocol were not reported. Study focused*

Study	Reason
urology : official journal of the Japanese Urological Association 11(2): 63-7	*on assessing tumors based on set CT criteria*
Li, Jing, Huang, Xiao, Wang, Lan et al. (2024) Role of Contrast-Enhanced Ultrasound With the Enhancement Pattern and Qualitative Analysis for Differentiating Hypovascular Solid Renal Lesions. Ultrasound in medicine & biology 50(2): 295-303	- Population *Population only with solid renal masses underwent CEUS*
Li, Xin, Liang, Ping, Guo, Mingzhou et al. (2013) Real-time contrast-enhanced ultrasound in diagnosis of solid renal lesions. Discovery medicine 16(86): 15-25	- Not OECD country *China*
Liang, Xia, Zeng, Xian-Tao, Hong, Zhi-Liang et al. (2024) Determinants of conventional and contrast-enhanced ultrasound diagnosis of fat-poor angiomyolipoma <5 cm. Frontiers in oncology 14: 1446801	- Not OECD country *China*
Ludwig, D R, Thacker, Y, Luo, C et al. (2023) CT-derived textural analysis parameters discriminate high-attenuation renal cysts from solid renal neoplasms. Clinical radiology 78(10): e782-e790	- Assessment tool do not match that specified in the protocol *no SPECT/CT or CEUS*
Mauro, M A, Balfe, D M, Stanley, R J et al. (1982) Computed tomography in the diagnosis and management of the renal mass. JAMA 248(21): 2894-6	- Review article but not a systematic review
Mazzei, Francesco Giuseppe, Mazzei, Maria Antonietta, Cioffi Squitieri, Nevada et al. (2014) CT perfusion in the characterisation of renal lesions: an added value to multiphasic CT. BioMed research international 2014: 135013	- End point do not match that specified in the protocol *Study reported on specific paraments of CT perfusion that could be used in diagnosing benign or malignant lesions such as permeability surface (PS), blood volume and blood flow. The sensitivity and specificity of PS was reported but unable to obtain contingency table values from data reported*
Millet, Ingrid, Doyon, Fernanda Curros, Hoa, Denis et al. (2011) Characterization of small solid renal lesions: can benign and malignant tumors be differentiated with CT?. AJR. American journal of roentgenology 197(4): 887-96	- Conference abstract
Miron Mombiela, Rebeca, Balschmidt, Trine, Birch, Carsten et al. (2025)	- Systematic review used as source of primary studies

Study	Reason
Diagnostic performance of contrast enhancement to differentiate benign and malignant renal lesions in CT and MRI: a systematic review and meta-analysis of diagnostic test accuracy (DTA) studies. Abdominal radiology (New York) 50(1): 360-378	*All relevant primary studies already reviewed in initial search. No additional new studies to include from this systematic review.*
Mlambo, Nompumelelo E; Dlamini, Nondumiso N M; Urry, Ronald J (2018) Correlation between radiological and histopathological findings in patients undergoing nephrectomy for presumed renal cell carcinoma on computed tomography scan at Grey's Hospital. SA journal of radiology 22(1): 1339	- Not OECD country *South Africa*
Mueller-Peltzer, K, Negrao de Figueiredo, G, Graf, T et al. (2019) Papillary renal cell carcinoma in contrast-enhanced ultrasound (CEUS) - A diagnostic performance study. Clinical hemorheology and microcirculation 71(2): 159-164	- Not a relevant study design *Aim of study to evaluate the observed enhancement features of histopathological confirmed papillary RCC*
Nazir, Z.; Maqsood, A.; Asgher, M.A. (2019) Detection of renal malignancy on multi-detector computed tomography in patients presented with hematuria. Pakistan Journal of Medical and Health Sciences 13(3): 845-847	- Not OECD country *Pakistan*
O'Connor, Stacy D, Pickhardt, Perry J, Kim, David H et al. (2011) Incidental finding of renal masses at unenhanced CT: prevalence and analysis of features for guiding management. AJR. American journal of roentgenology 197(1): 139-45	- End point do not match that specified in the protocol *Study focused on analysing renal masses incidentally detected during CT colonography, not on assessing the diagnostic accuracy of CT imaging*
Oh, Tae Hoon; Lee, Young Hwan; Seo, Ill Young (2014) Diagnostic efficacy of contrast-enhanced ultrasound for small renal masses. Korean journal of urology 55(9): 587-92	- Population *Population did not have CT/MRI prior. US was used prior as a baseline to detect renal masses.*
Patel, Neesha S, Poder, Liina, Wang, Zhen J et al. (2009) The characterization of small hypoattenuating renal masses on contrast-enhanced CT. Clinical imaging 33(4): 295-300	- Not a relevant study design *Case-control study (two-gate) involving patients with a small simple renal cyst and patients with renal cell carcinoma*
Rajan Harihar Prasad, P.K.A.; Toppo, S.K.; Ranjan, R. (2023) Study of Computed Tomography (CT) in Assessment in	- Not OECD country *India*

Study	Reason
Characterization of Renal Masses at a Tertiary Hospital. Journal of Cardiovascular Disease Research 14(9): 2273-2278	
Repeckaite, Gerta, Zviniene, Kristina, Jankauskiene, Justina et al. (2022) Small Renal Masses without Gross Fat: What Is the Role of Contrast-Enhanced MDCT?. Diagnostics (Basel, Switzerland) 12(2)	- End point do not match that specified in the protocol *Diagnostic outcomes (sensitivity, specificity, PPV and NPV) were reported for individual parameters of CT predictive of malignancy such as central scar, middle third and diameter of the tumour. Diagnostic outcomes for CT as a whole in diagnosis of renal masses was not reported*
Riccabona, M, Szolar, D, Preidler, K et al. (1999) Renal masses--evaluation by amplitude coded colour Doppler sonography and multiphasic contrast-enhanced CT. Acta radiologica (Stockholm, Sweden : 1987) 40(4): 457-61	- Reference standard in study does not match that specified in protocol *Reference standard includes histopathology and follow-up*
Rowe, Steven P, Gorin, Michael A, Gordetsky, Jennifer et al. (2015) Initial experience using 99mTc-MIBI SPECT/CT for the differentiation of oncocytoma from renal cell carcinoma. Clinical nuclear medicine 40(4): 309-13	- Not possible to calculate a contingency table from the data specified in the protocol
Rubenthaler, J, Paprottka, K, Marcon, J et al. (2016) Comparison of magnetic resonance imaging (MRI) and contrast-enhanced ultrasound (CEUS) in the evaluation of unclear solid renal lesions. Clinical hemorheology and microcirculation 64(4): 757-763	- Duplicate reference *Population and data reported is the same as in a study already included in the review*
Sanz, Enrique, Hevia, Vital, Gomez, Victoria et al. (2016) Renal Complex Cystic Masses: Usefulness of Contrast-Enhanced Ultrasound (CEUS) in Their Assessment and Its Agreement with Computed Tomography. Current urology reports 17(12): 89	- Population *CEUS used to differentiate between benign and malignant lesions and reference standard not pathological for all participants and CT is also used*
Sevcenco, S, Heinz-Peer, G, Ponhold, L et al. (2014) Utility and limitations of 3-Tesla diffusion-weighted magnetic resonance imaging for differentiation of renal tumors. European journal of radiology 83(6): 909-913	- Outcome to be predicted do not match that specified in the protocol *Sensitivity and specificity were only reported for the differentiation of papillary RCC from non-papillary RCC*
Shang, Wenwen; Hong, Guohui; Li, Wei (2023) MRI for the detection of small	- Systematic review used as source of primary studies

Study	Reason
malignant renal masses: a systematic review and meta-analysis. Frontiers in oncology 13: 1194128	
Shen, Lin, Li, Yanyan, Li, Na et al. (2019) Clinical utility of contrast-enhanced ultrasonography in the diagnosis of benign and malignant small renal masses among Asian population. Cancer medicine 8(18): 7532-7541	- Not OECD country *China*
Siddiqui, M.A., Ali, A., Khalid, K. et al. (2022) Diagnostic Accuracy of Multi-Detector CT for Evaluation of Renal Masses. Pakistan Journal of Medical and Health Sciences 16(3): 253-254	- Not OECD country *Pakistan*
Siddiqui, Tariq Saeed, Tariq, Asima, Rehman, Bushra et al. (2010) Accuracy of multiphase helical tomography in detection and characterisation of suspected renal masses using histopathological findings as gold standard. Journal of Ayub Medical College, Abbottabad : JAMC 22(3): 170-3	- Not OECD country *Pakistan*
Silverman, S G, Lee, B Y, Seltzer, S E et al. (1994) Small (< or = 3 cm) renal masses: correlation of spiral CT features and pathologic findings. AJR. American journal of roentgenology 163(3): 597-605	- Not possible to calculate a contingency table from the data specified in the protocol
Smith, F.W.; Hutchison, J.M.S.; Mallard, J.R. (1981) Renal cyst or tumour? Differentiation by whole-body nuclear magnetic resonance imaging. Diagnostic Imaging 50(2): 61-65	- Not a relevant study design *Case report*
Song, Cheryn, Min, Gyeong Eun, Song, Kanghyon et al. (2009) Differential diagnosis of complex cystic renal mass using multiphase computerized tomography. The Journal of urology 181(6): 2446-50	- Population *Population includes only cystic renal masses managed surgically which does not meet protocol criteria. Also, data is presented for each Bosniak category separately*
Songib, Nor-Azalina, Nazri, Mohammad, Yaakup, Nur Adura et al. (2013) Multiphase renal CT in the evaluation of renal masses: is the nephrographic phase necessary?. Clinical imaging 37(6): 1037-42	- Not OECD country *Malaysia*
Spahn, M, Portillo, F J, Michel, M S et al. (2001) Color Duplex sonography vs. computed tomography: accuracy in the	- End point do not match that specified in the protocol

Study	Reason
preoperative evaluation of renal cell carcinoma. European urology 40(3): 337-42	*Study assessed extent of tumour thrombosis of renal masses, as well as the localisation, size and lymph node metastasis*
Tamai, Hideyuki, Takiguchi, Yoshie, Oka, Masashi et al. (2005) Contrast-enhanced ultrasonography in the diagnosis of solid renal tumors. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 24(12): 1635-40	- Population *Not using CEUS in a population to differentiate solid renal massed from complex cysts*
Tello, R, Davison, B D, O'Malley, M et al. (2000) MR imaging of renal masses interpreted on CT to be suspicious. AJR. American journal of roentgenology 174(4): 1017-22	- Outcome to be predicted do not match that specified in the protocol *Study reported on the degree of enhancement and other characteristics of renal masses on MRI*
Thaiss, Wolfgang M, Bedke, Jens, Kruck, Stephan et al. (2019) Can contrast-enhanced ultrasound and acoustic radiation force impulse imaging characterize CT-indeterminate renal masses? A prospective evaluation with histological confirmation. World journal of urology 37(7): 1339-1346	- Not possible to calculate a contingency table from the data specified in the protocol
Tufano, Antonio, Antonelli, Luca, Di Pierro, Giovanni Battista et al. (2022) Diagnostic Performance of Contrast-Enhanced Ultrasound in the Evaluation of Small Renal Masses: A Systematic Review and Meta-Analysis. Diagnostics (Basel, Switzerland) 12(10)	- Population *Inclusion criteria for mode of initial diagnosis of small renal masses was ultrasound and not CT/MRI*
Tzortzakakis, Antonios, Gustafsson, Ove, Karlsson, Mattias et al. (2017) Visual evaluation and differentiation of renal oncocytomas from renal cell carcinomas by means of 99mTc-sestamibi SPECT/CT. EJNMMI research 7(1): 29	- Preceded by a related study *Tzortzakakis 2017 study only includes a sample of total study population included in Tzortzakakis 2022.*
Urraro, Fabrizio, Piscopo, Marco, Giordano, Nicoletta et al. (2024) Diagnostic Value of Contrast-Enhanced Ultrasound in Differentiating Malignant from Benign Small Renal Masses After CT/MRI. Journal of clinical medicine 13(21)	- End point do not match that specified in the protocol *Looking at differentiating between benign/malignant renal lesions rather than complex cysts/solid renal mass*
Voci, S L, Gottlieb, R H, Fultz, P J et al. (2000) Delayed computed tomographic characterization of renal masses:	- Reference standard in study does not match that specified in protocol

Study	Reason
preliminary experience. Abdominal imaging 25(3): 317-21	*Included pathologic confirmation in 25% of lesions and conventional CT showing no enhancement for the remaining lesions*
Wang, JingLing, Shi, JiaYu, Gao, Long et al. (2024) High-frame-rate contrast-enhanced ultrasound to differentiate between clear cell renal cell carcinoma and angiomyolipoma. BMC cancer 24(1): 659	- Population *CEUS used to differentiate between clear cell renal cell carcinoma and angiomyolipoma*
Warren, Hannah, Boydell, Anna-Rita, Reza, Abbas et al. (2022) Use of 99m Tc-sestamibi SPECT/CT for indeterminate renal tumours: a pilot diagnostic accuracy study. BJU international 130(6): 748-750	- Letter
Warren, Hannah, Fanshawe, Jack B, Mok, Valerie et al. (2024) Imaging modalities for characterising T1 renal tumours: A systematic review and meta-analysis of diagnostic accuracy. BJUI compass 5(7): 636-650	- Systematic review used as source of primary studies
Wei, Shu-Ping, Xu, Chao-Li, Zhang, Qing et al. (2017) Contrast-enhanced ultrasound for differentiating benign from malignant solid small renal masses: comparison with contrast-enhanced CT. Abdominal radiology (New York) 42(8): 2135-2145	- Not a relevant study design *Not a DTA study design of interest - comparing CEUS to contrast enhanced CT. CEUS used to differentiate benign from malignant.*
Wilson, Mitchell P, Katlariwala, Prayash, Murad, Mohammad H et al. (2020) Diagnostic accuracy of 99mTc-sestamibi SPECT/CT for detecting renal oncocytomas and other benign renal lesions: a systematic review and meta-analysis. Abdominal radiology (New York) 45(8): 2532-2541	- Reference standard in study does not match that specified in protocol *Pathology confirmation or contrast enhanced CEUS or two sonographers with expertise*
Wu, Hailan, Shi, Jiayu, Gao, Long et al. (2024) Qualitative and quantitative analysis of solid renal tumors by high-frame-rate contrast-enhanced ultrasound. Cancer imaging : the official publication of the International Cancer Imaging Society 24(1): 139	- Population *Ultrasound was used initially to identify renal mass rather than CT/MRI.*
Xia, Qingqing, Yuan, Xinchun, Huang, Meifeng et al. (2022) Contrast-enhanced Ultrasound for Diagnosis of Renal Cystic Mass. Current medical imaging 18(3): 292-298	- Not OECD country

Study	Reason
Xu, Zuo-Feng, Xu, Hui-Xiong, Xie, Xiao-Yan et al. (2010) Renal cell carcinoma and renal angiomyolipoma: differential diagnosis with real-time contrast-enhanced ultrasonography. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 29(5): 709-17	- Population *Patients had undergone baseline ultrasonography to identify suspicious renal masses rather than CT/MRI*
Yamashita, Y, Miyazaki, T, Hatanaka, Y et al. (1995) Dynamic MRI of small renal cell carcinoma. Journal of computer assisted tomography 19(5): 759-65	- Outcome to be predicted do not match that specified in the protocol *Diagnostic and clinical outcomes as per protocol were not reported. Study describes characteristic of tumours on MRI*
Yanagi, Masato, Kiriyama, Tomonari, Akatsuka, Jun et al. (2022) Differential diagnosis and prognosis of small renal masses: association with collateral vessels detected using contrast-enhanced computed tomography. BMC cancer 22(1): 856	- End point do not match that specified in the protocol *Study focused on the diagnostic accuracy of predictive biomarkers of CT such as overflowing beer sign (OBS), angular interface (AI) and collateral vessels.*
Yin, Qihua, Xu, Huiting, Zhong, Yanqi et al. (2022) Diagnostic performance of MRI, SPECT, and PET in detecting renal cell carcinoma: a systematic review and meta-analysis. BMC cancer 22(1): 163	- Systematic review used as source of primary studies
Yong, C; Teo, Y M; Jeevesh, K (2016) Diagnostic performance of contrast-enhanced ultrasound in the evaluation of renal masses in patients with renal impairment. The Medical journal of Malaysia 71(4): 193-198	- Not a relevant study design *Not a DTA design - patients selected were non-consecutive patients with indeterminant lesions picked up incidentally.*
Zarzour, Jessica G, Lockhart, Mark E, West, Janelle et al. (2017) Contrast-Enhanced Ultrasound Classification of Previously Indeterminate Renal Lesions. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 36(9): 1819-1827	- Population *Population group initially had CT/MRI/US to identify indeterminate lesions rather than CT/MRI alone.*
Zhang, Fan, Li, Rui, Li, Gang et al. (2019) Value of Contrast-Enhanced Ultrasound in the Diagnosis of Renal Cancer and in Comparison With Contrast-Enhanced Computed Tomography: A Meta-analysis. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 38(4): 903-914	- Population *Target condition is malignant vs. benign rather than solid renal mass vs. cystic*

Study	Reason
Zhou, Xiang, Yan, Feng, Luo, Yan et al. (2011) Characterization and diagnostic confidence of contrast-enhanced ultrasound for solid renal tumors. Ultrasound in medicine & biology 37(6): 845-53	- Reference standard in study does not match that specified in protocol *Reference standard was surgical specimens or MRI*
Zhu, Hongjing, Yang, Bo, Dong, Aisheng et al. (2020) Dual-Phase 99mTc-MIBI SPECT/CT in the Characterization of Enhancing Solid Renal Tumors: A Single-Institution Study of 147 Cases. Clinical nuclear medicine 45(10): 765-770	- Not OECD country
Zokalj, Ivan, Marotti, Miljenko, Saghir, Hussein et al. (2012) Multiphase computed tomography of malignant kidney tumors: radiologic-pathologic comparison. Acta clinica Croatica 51(4): 563-71	- Not OECD country *Croatia*

Economic references excluded at full text (n = 6)

Table 17: Excluded economic studies

Study	Reason
Gassert, Felix, Schnitzer, Moritz, Kim, Su Hwan et al. (2021) Comparison of Magnetic Resonance Imaging and Contrast-Enhanced Ultrasound as Diagnostic Options for Unclear Cystic Renal Lesions: A Cost-Effectiveness Analysis. Ultraschall in der Medizin (Stuttgart, Germany : 1980) 42(4): 411-417	- Non-protocol country setting (US healthcare perspective)
Oh, Aaron, Bhardwaj, Lokesh, Cacciamani, Giovanni et al. (2023) Cost-effectiveness of Contrast-Enhanced Ultrasound for Diagnosis and Active Surveillance of Complex Cystic Renal Lesions. Urology practice 10(1): 11-19	- Non-protocol country setting (US healthcare perspective) - Non-protocol cost perspective (third party payer perspective) - Non-protocol intervention/comparator (active surveillance instead of diagnosis)
Patel, Bhavik N, Boltyenkov, Artem T, Martinez, Maria G et al. (2020) Cost-effectiveness of dual-energy CT versus multiphasic single-energy CT and MRI for characterization of incidental indeterminate renal lesions. Abdominal radiology (New York) 45(6): 1896-1906	- Non-protocol country setting (US healthcare perspective)

Study	Reason
Runtemund, Jasmin, Rubenthaler, Johannes, von Munchhausen, Niklas et al. (2022) Diagnostic Workup for Patients with Solid Renal Masses: A Cost-Effectiveness Analysis. Cancers 14(9)	- Non-protocol country setting (US healthcare perspective) - Non-protocol intervention/comparator (compares CEUS to CT and MRI)
Su, Zhuo T, Patel, Hiten D, Huang, Mitchell M et al. (2021) Cost-effectiveness Analysis of 99mTc-sestamibi SPECT/CT to Guide Management of Small Renal Masses. European urology focus 7(4): 827-834	- Non-protocol country setting (US healthcare perspective)
Zbroja, Monika, Kuczynska, Maryla, Drelich, Katarzyna et al. (2024) Contrast-Enhanced Ultrasound in the Diagnosis of Solid Renal Lesions. Journal of clinical medicine 13(13)	- Not economic evaluation

Appendix K– Research recommendations

K1.1 Research recommendation

What are the most accurate and cost-effective combinations and sequences of diagnostic approaches (imaging and biopsy) for differentiating between benign and malignant renal lesions in people with suspected RCC?

K.1.1.1 Why this is important

There are several novel imaging approaches that can be used in differentiating between benign and malignant renal lesions in people with suspected RCC. However, there is a lack of evidence on the diagnostic accuracy and cost effectiveness of different combinations and sequences of these imaging approaches in differentiating between benign and malignant renal lesions.

K.1.1.2 Rationale for research recommendations

Table 18: Rationale for research recommendation

Importance to 'patients' or the population	Having an effective imaging approach could limit unnecessary surgery or biopsy where the lesion is found to be benign sooner. It could also provide access to treatments or active surveillance where the lesion is found to be malignant.
Relevance to NICE guidance	There have been several imaging techniques considered in the development of NICE's kidney cancer guideline however there is a lack of data comparing different imaging approaches for the purpose of identifying the most accurate and cost effective approach.
Relevance to the NHS	There are several imaging techniques for clinicians to choose from which could cause difficulty in selecting the best approach. Therefore, it would be helpful if clinicians had more evidence-based guidance to help them with decision making. The outcome would also have downstream effects on diagnosis, treatment and ultimately a person's morbidity. It may also help reduce resource impact for the NHS if certain imaging approaches are found to be more cost-effective or it may predict additional imaging needs in the NHS for people with suspected RCC.
National priorities	Low
Current evidence base	Minimal data was identified for different combinations and sequences of imaging in differentiating between benign and malignant tumours.
Equality considerations	None known

K.1.1.3 Modified PICO table

Table 19: Modified PICO table

Population	Adults (18 years or over) with suspected RCC and for whom diagnostic imaging is suitable
Index test	Any of the following imaging types or core biopsy in different combinations and sequences: • CT (with or without contrast) • MRI (with or without contrast) • Contrast-enhanced ultrasonography (US) for differentiating between solid masses and complex cysts • ^{99m}Tc-sestamibi SPECT/CT • Core biopsy
Reference standard	Pathological confirmation of RCC from surgery
Outcome	Diagnostic accuracy outcomes: • Sensitivity and specificity • Positive and negative likelihood ratios Additional clinical outcomes from test and treat studies: • Need for biopsy (dichotomous outcome) • Overall survival (time to event data) • Quality of life Cost effectiveness
Study design	Diagnostic accuracy cross-sectional studies and cohort studies.
Timeframe	Low
Additional information	None