National Institute for Health and Care Excellence

Kidney Cancer: diagnosis and management

[G] Evidence review for the criteria for genetic assessment and management of RCC associated with heritable renal cell carcinoma syndromes

NICE guideline [number]

Evidence review underpinning recommendations 1.16.1 to 1.16.3, 1.16.5, 1.17.1 to 1.17.7, 1.18.1 to 1.18.3, 1.20.1 to 1.20.5 in the NICE guideline

September 2025

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: xxx

Contents

1 Genetic assessment and management of RCC in people with heritable renal cell carcinoma syndromes

1.1 Review questions

1 To inform the need for genetic assessment in adults with confirmed renal cell carcinoma (RCC), which of the following risk factors are associated with hereditary RCC:

- age at diagnosis ≤ 46 years,
- bilateral or multifocal tumours/cysts
- family history
- syndromic manifestations of a hereditary renal cancer predisposition syndrome
- histological subtype e.g. fumarate hydratase-deficient RCC, succinate dehydrogenase deficient RCC?

2 What is the clinical and cost effectiveness of:

- different interventions (surgical or non-surgical) or active surveillance, compared to each other and
- different follow up strategies compared to each other for adults with heritable renal cell carcinoma?

1.1.1 Introduction

Some individuals with renal cell carcinoma (RCC) may have a heritable mutation in a known gene that predisposes them to RCC, and the criteria for germline testing have been described in the National genomic test directory for rare and inherited diseases. Since the criteria listed in this directory are regularly updated and new criteria are added as new variants are identified, it was decided that rather than reviewing the evidence for question 1 above, it would be more useful to cross refer to this directory instead. Therefore, this review will focus on question 2, but the committee will discuss and make recommendations on both questions.

People with heritable renal cancer syndromes are more likely to develop multiple tumours throughout their lifetimes, and treatment needs to balance the risk of metastasis with the preservation of renal function. Management may also vary depending on the specific syndrome, with some conditions such as hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC) being associated with more aggressive tumours.

There are resources available that suggest optimum management of heritable renal cancer syndromes, such as UK Cancer Genetics Group and ERN Genturis guidelines, however, these do not specifically focus on the management of suspected or confirmed RCC in this population. This review aims to address this gap.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria for the management of hereditary renal cell carcinoma

Population	Adults with heritable renal cancer susceptibility syndromes and: • Suspicious renal lesions on imaging or • Confirmed RCC through biopsy or surgical pathology Exclusions: People with metastatic RCC

Interventions	**Non-pharmacological treatments:**
	• Active surveillance or delayed interventions
	• Nephron-sparing treatments:
	  ○ partial nephrectomy
	  ○ thermal ablation
	  ○ SABR
	• radical (total) nephrectomy
	Follow-up strategies:
	• Any follow-up strategies

Comparator	• Different non-pharmacological management approaches for heritable RCC compared with each other • Different follow-up approaches compared with each other • No comparison (where no comparative evidence is identified)
Outcomes	**Survival outcomes:** • Overall survival (time to event data) • Cancer-specific survival (time to event data) • Metastasis-free survival (time to event data) **Recurrence outcomes:** This outcome will only be considered if no data on metastases-free survival is available. • Distant recurrence (dichotomous data; latest time point) **Adverse events/long term consequences:** • New onset chronic kidney disease (stages 4 to 5; dichotomous data; latest time point) • Need for dialysis or renal transplant (dichotomous data; latest time point) **Quality of life outcomes:** • EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30) (dichotomous or continuous data) • EuroQol-5 dimensions (EQ-5D; dichotomous or continuous data)
Study type	• Systematic reviews of RCTs and primary RCTs are preferred. • If RCTs are not available, systematic reviews of observational studies and primary observational studies (including cohort and case series) will be considered.

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 and the methods document.

Heritable RCC predisposition syndromes of particular interest included:

- BAP1 tumour predisposition Syndrome BAP1-TPDS

- Birt-Hogg-Dubé syndrome (BHDS)
- Hereditary leiomyomatosis and renal cell cancer (HLRCC)
- Hereditary papillary renal Carcinoma (HPRC)
- Hereditary paraganglioma/ Pheochromocytoma (PGL/PCC)
- Tuberous sclerosis complex (TSC)
- von Hippel-Lindau (VHL).

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

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 24/02/2025. The following databases were searched: Cochrane CENTRAL (Wiley), Cochrane CDSR (Wiley), Embase (Ovid) and Medline ALL (Ovid). Full search strategies for each database are provided in Appendix B. Limits were applied to remove animal papers, non-english language papers and conference abstracts. Filters were used to limit to OECD countries, systematic reviews, randomised controlled trials and observational studies

The searches for the cost effectiveness evidence were run on 03/03/2025. The following databases were searched: The following databases were searched: Econlit (Ovid), Embase (Ovid), International Health Technology Assessment Database (INAHTA), Medline ALL (Ovid). Limits were applied to remove animal papers, non-english language papers and conference abstracts. Filters were used to limit to OECD countries, cost utility, health state utility and cost effectiveness studies.

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

1.1.3.2 Protocol deviations

1 The review was only able to identify non-comparative evidence, and therefore it was not possible to pool the evidence using meta-analysis or to carry out GRADE to assess certainty of the evidence. As a result, outcome data was reported for each study separately in section 1.1.6 Summary of the effectiveness evidence along with the risk of bias and applicability for each study. Results were also summarised narratively in section 1.1.11 Evidence statements.

2 For the outcome of new onset kidney disease, events were recorded where participants developed stage 4 or 5 CKD. This was a deviation from stage 3a to 5 CKD in the protocol and was informed by committee input that stages 4 and 5 are more relevant due to their increased clinical significance.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 3,593 references (see appendix B for the literature search strategy), and one study was identified by the committee.

These 3,594 references were screened at title and abstract level against the review protocol, with 3,524 excluded at this level. 10% of references were screened separately by two reviewers with 100% agreement.

The full texts of 70 case series were ordered for closer inspection. 26 of these studies met the criteria specified in the review protocol (appendix A). For a summary of the 26 included studies see Table 2.

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

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

1.1.4.2 Excluded studies

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

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of studies included in the effectiveness evidence

Study details	Population	Intervention	Follow-up frequency	Outcomes	Risk of bias
Allasia (2017) N=9 Follow-up: median 102 months Location: Italy	People with Suspected VHL and RCC [People received genetic testing upon access to the VHL unit, and the report did not state that any participants tested negative]	Radiofrequency ablation	Year 1: every 3 months Year 2: every 6 months Year 3 onwards: every year	Overall survival Cancer-specific survival New-onset CKD	High
Bodard (2022) N=6 Follow-up: median 74 months Location: France	People with BHDS who underwent thermal ablation for a renal tumour	Percutaneous thermal ablation	Year 1: at 2, 6, and 12 months Year 2 onwards: every year	Overall survival Cancer-specific survival Distant recurrence New-onset CKD Need for dialysis or renal transplant	Moderate
Bratslavsky (2008) N=11 Follow-up: median 25 months Location: The US	People who underwent at least 3 partial nephrectomies on the same renal unit	Salvage partial nephrectomy	Not reported	Overall survival Cancer-specific survival Distant recurrence Need for dialysis or renal transplant	High

Study details	Population	Intervention	Follow-up frequency	Outcomes	Risk of bias
Chan (2022) N=17 Follow-up: median 79 months Location: UK	Adults with VHL with T1a RCC (<4 cm)	Image-guided ablation (radiofrequency ablation, cryoablation, irreversible electroporation)	Year 1: months 1, 3, 6, and 12 Year 2 onwards: every 6 months	Overall survival Cancer-specific survival Metastasis-free survival Distant recurrence New-onset CKD Need for dialysis or renal transplant	Moderate
Drachenberg (2004) N=32 Follow-up: median 33.7 months Location: The US	People with small hereditary central renal tumours	Nephron-sparing surgery	Not reported	Overall survival Cancer-specific survival Distant recurrence Need for dialysis or renal transplant	High
Frydenberg (1993) N=19 Follow-up: mean 5 years Location: The US	People with VHL and RCC	Partial nephrectomy Radical nephrectomy Radical nephrectomy and contralateral partial nephrectomy	At least yearly	Overall survival Cancer-specific survival Distant recurrence	High
Gaillard (2020) N=10 Follow-up: mean 7.5 years Location: France	People with a history of bilateral, multifocal or early occurring renal tumours before 60 years, who underwent at least 1 percutaneous thermo-ablative intervention for a renal tumour	Thermal ablation (cryotherapy and radiotherapy)	Year 1: either months 1 or 3, then month 9 Year 2 onwards: every year	Overall survival Cancer-specific survival Distant recurrence New-onset CKD	High
Gill (2014) N=12	People with RCC and proven SDH mutation or	Total nephrectomy Partial nephrectomy	Not reported	Overall survival Cancer-specific survival	High

Study details	Population	Intervention	Follow-up frequency	Outcomes	Risk of bias
Follow-up: mean 55 months Location: North America, Europe, Asia, Australia	suspected SDH deficiency on the basis of morphology, immunohistochemistry, or a personal or family history of paragangliomas or SDH-deficient GIST.	Total nephrectomy and contralateral wedge resection		Distant recurrence	
Grubb (2007) N=15 [non-metastatic only] Follow-up: median 34 months Location: The US	People with risk of HLRCC with renal tumours	Radical nephrectomy Partial nephrectomy Both radical and partial nephrectomy for bilateral lesions	Not reported	Overall survival Cancer-specific survival Distant recurrence	High
Gupta (2010) N=58 Follow-up: median 45 months Location: The US	People with either VHL, BHD, or HPRC with multifocal renal masses where the largest renal tumour was greater than 4 cm	Partial nephrectomy	Year 1: month 3 Year 2 onwards: every year	Overall survival Cancer-specific survival Metastasis-free survival Distant recurrence	High
Hes (1999) N=8 Follow-up: Radical nephrectomy - mean 171 months Partial nephrectomy – mean 30 months Location: The Netherlands	People with VHL and RCC	Partial nephrectomy Radical nephrectomy	Every year	New-onset CKD Need for dialysis or renal transplant	High
Iwamoto (2011)	People with VHL and RCC	Percutaneous radiofrequency ablation	Year 1: week 1, months 3, 6, 12	Overall survival	Moderate

Study details	Population	Intervention	Follow-up frequency	Outcomes	Risk of bias
N=7 Follow-up: mean 22 months Location: Japan			Year 2 onwards: every 6 months	Cancer-specific survival Distant recurrence	
Johnson (2008) N=47 Follow-up: median 56 months Location: The US	People with recurrent kidney tumours	Repeat partial nephrectomy	Not reported	Overall survival Distant recurrence Need for dialysis or renal transplant	High
Kirste (2022) N=7 Follow-up: median 43 months Location: Germany	People with VHL and a progressive suspected RCC ≥1.5 cm	Stereotactic body radiotherapy	Every 3 to 6 months	Overall survival Cancer-specific survival New-onset CKD Need for dialysis or renal transplant	Low
Lund (1994) N=10 Follow-up: mean 62 months Location: The US	People with VHL and asymptomatic renal masses	Partial nephrectomy Partial nephrectomy and contralateral radical nephrectomy	Not reported	Overall survival Cancer-specific survival Distant recurrence Need for dialysis or renal transplant	High
Matsui (2019) N=6 Follow-up: median 54 months Location: Japan	People with BHDS who underwent percutaneous thermal ablation for RCC	Percutaneous thermal ablation	Year 1: months 1, 3, and 6 Year 2: every 6 to 12 months	Overall survival Cancer-specific survival Distant recurrence New-onset CKD Need for dialysis or renal transplant	Moderate
Matsukawa (2024) N=14	People with VHL who underwent percutaneous	Percutaneous cryoablation	Not reported	Distant recurrence	High

Study details	Population	Intervention	Follow-up frequency	Outcomes	Risk of bias
Follow-up: median 57.5 months Location: Japan	cryoablation for small RCCs				
Novick (1992) N=9 Follow-up: mean 7.2 years Location: The US	People with VHL and localised bilateral RCC	Nephron-sparing surgery	Not reported	Overall survival Cancer-specific survival Distant recurrence Need for dialysis or renal transplant	High
Osman (2023) N=53 Follow-up: mean 30.4 months Location: Denmark, France, the Netherlands, the UK	People with inherited RCC syndromes and localised cT1aN0M0 or cT1bN0M0 tumours	Percutaneous cryoablation	Not reported	Overall survival Cancer-specific survival Metastasis-free survival Distant recurrence	Moderate
Park (2010) N=11 Follow-up: mean 23 months Location: Korea	People with VHL and renal tumour	Percutaneous radiofrequency ablation	Year 1: months 1, 6, 12 Year 2: every 6 months Year 3: every 12 months	New-onset CKD	High
Ploussard (2007) N=16 Follow-up: median 100 months Location: France	People with VHL and renal tumour	Partial nephrectomy Active surveillance	Every 6 months	Cancer-specific survival Distant recurrence New onset CKD Need for dialysis or renal transplant	High
Schuhmacher (2019) N=41 Follow-up: mean 52.2 months	People with VHL and radiologically detected ccRCC with a minimum of 3 consecutive MRIs	Active surveillance Partial nephrectomy	Not reported	Distant recurrence	High

Study details	Population	Intervention	Follow-up frequency	Outcomes	Risk of bias
Location: Germany	performed with no greater gap than 3 years				
Shinohara (1995) N=5 Follow-up: median 61 months Location: Japan	People with RCC and family history of VHL	Nephron-sparing surgery	Between 3- and 6-month intervals after surgery	Distant recurrence Need for dialysis or renal transplant	High
Steinbach (1995) N=65 Follow-up: mean 68 months Location: The US	People with VHL who had surgery for RCC	Radical nephrectomy Nephron-sparing surgery	Not reported	Cancer-specific survival Distant recurrence New-onset CKD	High
Wessendorf (2021) N=9 Follow-up: 34 months Location: Germany	People with VHL who underwent radiofrequency ablation for RCC where tumour growth was >0.5 cm/year or had a tumour diameter >3 cm	Repeat percutaneous radiofrequency ablation	4 to 6 months after every ablation and every 6 months thereafter	Overall survival Need for dialysis or renal transplant	Moderate
Yang (2013) N=14 Follow-up: mean 37.6 months Location: The US	People with VHL with bilateral RCC who underwent 1 or more salvage ablation	Thermal ablation (percutaneous cryoablation, radiofrequency ablation, laparoscopic cryoablation)	Year 1: day 1, and months 3, 6, and 12 Year 2: every year	Overall survival Cancer-specific survival Distant recurrence Need for dialysis or renal transplant	High

BHDS, Birt-Hogg Dube Syndrome; ccRCC, clear-cell renal cell carcinoma; CKD, chronic kidney disease; HLRCC, hereditary leiomyomatosis and renal cell cancer syndrome; HPRC, hereditary papillary renal cell carcinoma; RCC, renal cell carcinoma; VHL, von-Hippel Lindau

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

1.1.6.1 Management of heritable RCC

Table 3 Summary of effectiveness for people with VHL receiving active surveillance

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Ploussard (2007) n=3 Follow-up: median 100 months	Active surveillance [Participants did not undergo surgery for initial tumour as size <3 cm]	Every 6 months	Not reported [Indication for surgery was larger than 3 cm]	Distant recurrence: 0 events	High	Directly applicable
Schuhmacher (2019) n=24 Follow-up: mean 52.2 months	Active surveillance [Participants did not undergo surgery for initial tumour]	Not reported	Not reported [Threshold to surgery was 4 cm]	Distant recurrence: 0 events	High	Directly applicable

Table 4 Summary of effectiveness for people with VHL receiving partial nephrectomy

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Bratslavsky (2008) n=11	Salvage partial nephrectomy	Not reported	Not reported	OS: 0 participants died CSS: 0 participants died	High	Partially applicable

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Follow-up: median 25 months				Distant recurrence: 0 events Dialysis or renal transplant: 2 events		
Frydenberg (1993) n=9 Follow-up: mean 5 years	Partial nephrectomy	At least yearly	Not reported	OS: 0 participants died CSS: 0 participants died Distant recurrence: 0 events	High	Directly applicable
Hes (1999) n=5 Follow-up: mean 30 months	Partial nephrectomy	Every year	Median 2.6 cm (range 1 to 5.5 cm)	New-onset CKD: 0 events	High	Directly applicable
Lund (1994) n=9 Follow-up: mean 49 months	Partial nephrectomy	Not reported	Not reported separately for each intervention	OS: 2 participants died CSS: 1 participant died Distant recurrence: 2 events Dialysis or renal transplant: 0 events	High	Directly applicable
Novick (1992) n=9 Follow-up: mean 7.2 years	Nephron-sparing surgery	Not reported	Not reported	OS: 1 participant died CSS: 1 participant died Distant recurrence: 2 events Dialysis or renal transplant: 2 events	High	Directly applicable
Ploussard (2007) n=13 Follow-up: median 100 months	Partial nephrectomy	Every 6 months	Mean 3.32 cm (range 2.2 to 5.9 cm)	CSS: 0 participants died Distant recurrence: 0 events New-onset CKD: 0 events Dialysis or renal transplant: 0 events	High	Directly applicable

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Schuhmacher (2019) n=17 Follow-up: mean 52.2 months	Partial nephrectomy	Not reported	Mean 41.3 cm^3	Distant recurrence: 0 events	High	Directly applicable
Shinohara (1995) n=5 Follow-up: median 61 months	Nephron-sparing surgery	Between 3-to-6-month intervals after surgery	Range 3 to 7.5 cm	Distant recurrence: 0 events Dialysis or renal transplant: 0 events	High	Directly applicable
Steinbach (1995) n=49 Follow-up: mean 68 months	Nephron-sparing surgery	Not reported	Not reported	CSS: 10-year rate = 81% Distant recurrence: 2 events New-onset CKD: 7 events	High	Partially directly applicable

CKD, chronic kidney disease; CSS, cancer-specific survival; OS, overall survival

Table 5 Summary of effectiveness for people with VHL receiving thermal ablation

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Allasia (2017) N=9 Follow-up: median 102 months	Radiofrequency ablation	Year 1: every 3 months Year 2: every 6 months Year 3 onwards: every year	Median 2.5 (IQR 2 to 3 cm)	OS: 0 participants died CSS: 0 participants died New-onset CKD: 0 events	High	Directly applicable

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Chan (20220 N=10 Follow-up: median 79 months	Radiofrequency ablation n=11 Cryoablation: n=38 Irreversible electroporation: n=9	Year 1: months 1, 3, 6, and 12 Year 2 onwards: every 6 months	Mean 2.1 cm (SD 0.92)	OS: rate 90% (95% CIs 47.3 to 98.5); 1 participant died CSS: rate 100% MFS: rate 100% New onset CKD: 0 events Dialysis or renal transplant: 1 event	Moderate	Partially directly applicable
Iwamoto (2011) n=7 Follow-up: mean 22 months	Percutaneous radiofrequency ablation	Year 1: week 1, and months 3, 6, and 12 Year 2 onwards: every 6 months	Mean 1.9 cm (1 to 3.6)	OS: 1 participant died CSS: 0 participants died Distant recurrence: 0 events New-onset CKD: 0 events	Moderate	Directly applicable
Matsukawa (2024) n=14 Follow-up: 54.5 months	Percutaneous cryoablation	Not reported	Median 2.3 (IQR 1.775 to 2.725)	Distant recurrence: 0 events	High	Directly applicable
Osman (2023) n=41 Follow-up: mean 30.4 months	Percutaneous cryoablation	Not reported	Mean 2.46 cm (SD 1)	OS: 1 participant died CSS: 1 participant died Distant recurrence: 1 event	Moderate	Directly applicable
Park (2010) n=11 Follow-up: mean 23 months	Percutaneous radiofrequency ablation	Year 1: months 1, 6, 12 Year 2: every 6 months Year 3: every 12 months	Mean 2.3 cm (range 0.8 to 5.9 cm)	New-onset CKD: 0 events	High	Partially directly applicable

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Wessendorf (2021) n=9 Follow-up: 34 months	Repeat percutaneous radiofrequency ablation	4 to 6 months after every ablation and every 6 months thereafter	Mean 3.29 cm (SD 0.86 cm)	OS: 1 participant died Dialysis or renal transplant: 0 events	Moderate	Directly applicable
Yang (2013) N=14 Follow-up: mean 37.6 months	Percutaneous cryoablation (13 procedures) Radiofrequency ablation (14 procedures) Laparoscopic cryoablation (3 procedures)	Year 1: day 1, and months 3, 6, and 12 Year 2: every year	Mean 2.64 cm (SD 1 cm)	OS: 92%; 1 participant died CSS: 100%; 0 participants died Distant recurrence: 0 events Dialysis or renal transplant: 0 events	High	Directly applicable

CKD, chronic kidney disease; CSS, cancer-specific survival; MFS, Metastasis-free survival; OS, overall survival

Table 6 Summary of effectiveness for people with VHL receiving SABR

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Kirste (2022) n=7 Follow-up: median 43 months	Stereotactic body radiotherapy	Every 3 to 6 months	Median 2.8 cm (range 1.9 to 3.5 cm)	OS: 2-year rate 85.7% CSS: 2-year rate 100% New-onset CKD: 0 events Dialysis or renal transplant: 0 events	Low	Directly applicable

CKD, chronic kidney disease; CSS, cancer-specific survival; OS, overall survival

Table 7 Summary of effectiveness for people with VHL receiving radical nephrectomy

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Frydenberg (1993) N=19 Follow-up: mean 5 years	Radical nephrectomy	At least yearly	Not reported	OS: 4 participants died CSS: 4 participants died Distant recurrence: 4 events	High	Directly applicable
Hes (1999) n=3 Follow-up: mean 171 months	Radical nephrectomy	Every year	Median 2.3 cm (IQR 1.4 to 14 cm)	Dialysis or renal transplant: 2 events	High	Directly applicable
Steinbach (1995) n=16 Follow-up: mean 68 months	Radical nephrectomy	Not reported	Not reported	CSS: 10-year rate 36% New-onset CKD: 8 events	High	Partially directly applicable

CKD, chronic kidney disease; CSS, cancer-specific survival; OS, overall survival

Table 8 Summary of effectiveness for people with VHL receiving both partial and radical nephrectomy

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Frydenberg (1993) n=4 Follow-up: mean 5 years	Radical nephrectomy and contralateral partial nephrectomy	At least yearly	Not reported	OS: 2 participants died CSS: 2 participants died Distant recurrence: 4 events	High	Directly applicable
Lund (1994) n=1 Follow-up: mean 99 months	Radical nephrectomy and contralateral partial nephrectomy	Not reported	Not reported separately for each intervention	OS: 0 participants died CSS: 0 participants died Distant recurrence: 0 events Need for dialysis or renal transplant: 0 events	High	Directly applicable

CSS, cancer-specific survival; OS, overall survival

Table 9 Summary of effectiveness for people with BHDS receiving thermal ablation

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Bodard (2022) n=6 Follow-up: median 74 months	Percutaneous thermal ablation	Year 1: months 2, 6, and 12 Year 2 onwards: every year	Mean 2.1 cm (SD 1.1 cm)	OS: 0 participants died CSS: 0 participants died Distant recurrence: 0 events New-onset CKD: 0 events Dialysis or renal transplant: 0 events	Moderate	Directly applicable

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Matsui (2019) n=6 Follow-up: median 54 months	Thermal ablation	Year 1: months 1, 3, and 6 Year 2: every 6 to 12 months	Mean 1.39 cm (SD 0.46 cm)	OS: 0 participants died CSS: 0 participants died Distant recurrence: 0 events New-onset CKD: 0 events Dialysis or renal transplant: 0 events	Moderate	Directly applicable

CKD, chronic-kidney disease; CSS, cancer-specific survival; OS, overall survival

Table 10 Summary of effectiveness for people with HLRCC receiving partial nephrectomy

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Grubb (2007) n=2 Follow-up: median 34 months	Partial nephrectomy	Not reported	Median 1.5 cm (range 1.5 to 1.5 cm)	OS: 0 participants died CSS: 0 participants died Distant recurrence: 0 events	High	Directly applicable

CSS, cancer-specific survival; OS, overall survival

Table 11 Summary of effectiveness for people with HLRCC receiving radical nephrectomy

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Grubb (2007) n=12 Follow-up: median 34 months	Radical nephrectomy	Not reported	Median 7 cm (range 2.3 to 10 cm)	OS: 4 participants died CSS: 4 participants died Distant recurrence: 6 events	High	Directly applicable

CSS, cancer-specific survival; OS, overall survival

Table 12 Summary of effectiveness for people with HLRCC receiving both partial and radical nephrectomy

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Grubb (2007) n=1 Follow-up: median 34 months	Radical and partial nephrectomy	Not reported	Not reported	OS: 0 participants died CSS: 0 participants died Distant recurrence: 1 event	High	Directly applicable

CSS, cancer-specific survival; OS, overall survival

Table 13 Summary of effectiveness for people with SDH-deficient RCC receiving radical nephrectomy

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Gill (2014) n=5 Follow-up: median 8 months	Radical nephrectomy	Not reported	Mean 51 mm (range 7 to 90) [All participants]	OS: 0 participants died CSS: 0 participants died Distant recurrence: 1 event	High	Directly applicable

CSS, cancer-specific survival; OS, overall survival

Table 14 Summary of effectiveness for people with SDH-deficient RCC receiving partial nephrectomy

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Gill (2014) n=5 Follow-up: median 3 months	Partial nephrectomy	Not reported	Mean 51 mm (range 7 to 90) [All participants]	OS: 1 participant died CSS: 1 participant died Distant recurrence: 1 event	High	Directly applicable

CSS, cancer-specific survival; OS, overall survival

Table 15 Summary of effectiveness for people with SDH-deficient RCC receiving radical nephrectomy and contralateral wedge resection

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Gill (2014) n=2 Follow-up: median 40 months	Radical nephrectomy and contralateral wedge resection	Not reported	Mean 51 mm (range 7 to 90) [All participants]	OS: 0 participants died CSS: 0 participants died Distant recurrence: 0 events	High	Directly applicable

CSS, cancer-specific survival; OS, overall survival

Table 16 Summary of effectiveness for people with mixed hereditary RCC receiving partial nephrectomy

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Drachenberg (2004) n=32 Follow-up: median 33.7 months	Nephron-sparing surgery	Not reported	Mean 3.2 cm (range 1.5 to 7.5 cm)	OS: 0 participants died CSS: 0 participants died Distant recurrence: 0 events Dialysis or renal transplant: 1 event	High	Partially directly applicable
Gupta (2010) n=58 Follow-up: median 45 months	Partial nephrectomy	Year 1: 3 months Year 2 onwards: every year	Mean 5.3 cm (range 4 to 13 cm)	OS: 5-year rate 93.3% CSS: 5-year rate 96.7% MFS: 5-year rate 96.5%; 2 distant recurrences	High	Partially directly applicable

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Johnson (2008) n=47 Follow-up: median 56 months	Repeat partial nephrectomy	Not reported	Median 3.5 cm (range 0.9 to 8 cm)	OS: 1 participant died Distant recurrence: 2 events Dialysis or renal transplant: 3 events	High	Partially directly applicable

CSS, cancer-specific survival; MFS, metastasis-free survival; OS, overall survival

Table 17 Summary of effectiveness for people with mixed hereditary RCC receiving thermal ablation

Study	Intervention	Follow-up frequency	Tumour size	Outcomes	Risk of bias	Directness
Gaillard (2020) n=10 Follow-up: mean 7.5 years	Thermal ablation: Cryotherapy (24 treatments) Radiotherapy (8 treatments)	Year 1: either months 1 or 3, then 9 months Year 2 onwards: every year	Mean 1.35 cm (SD 0.9 cm)	OS: 1 participant died CSS: 0 participants died Distant recurrence: 1 distant recurrence New-onset CKD: 1 event	High	Partially directly applicable
Osman (2023) n=53 Follow-up: mean 30.4 months	Percutaneous cryoablation	Not reported	Mean 2.46 cm (SD 1 cm)	OS: 5-year rate 90.9% (95% CI 51% to 99%); 1 participant died CSS: 5-year rate 90.9% (95% CI 51% to 99%); 1 participant died MFS: 5-year rate 96.4% (95% CI 77% to 99%); 1 event	Moderate	Directly applicable

CSS, cancer-specific survival; MFS, metastasis-free survival; OS, overall survival

1.1.6.2 Evidence comparing different follow-up strategies

No evidence was identified assessing different follow-up strategies

1.1.7 Economic evidence

A literature search was conducted to identify published economic evaluations of relevance to this review question (see appendix B). This search retrieved 179 studies, of which one study was included at title and abstract screening but was excluded at full text screening.

1.1.7.1 Excluded studies

One study was excluded at full text review (see appendix J for study details and reasons for exclusion).

1.1.8 Summary of included economic evidence

No economic evidence was identified for this review question.

1.1.9 Economic model

No original economic modelling was conducted for this review.

1.1.10 Unit costs

Unit costs of interventions in the scope of this review are listed in Table 18.

Table 18: Unit costs

Resource	Unit cost	Source
Open nephrectomy	£10,142.10	NHS Cost Collection (2024). Weighted average of codes LB61C-G, Major, Open or Percutaneous, Kidney or Ureter Procedures, 19 years and over
Laparoscopic nephrectomy	£9,970.10	NHS Cost Collection (2024). Weighted average of codes LB62C-D, Major Laparoscopic, Kidney or Ureter Procedures, 19 years and over
Robot-assisted nephrectomy	£10,172.87	Ratio of robotic to laparoscopic partial nephrectomy cost estimated from Camp et al. (2018), calculated as £4,444 / £4,356 = 1.02. Ratio applied to the laparoscopic nephrectomy unit cost to estimate robotic nephrectomy unit cost.
CT preparation for SABR therapy	£1,770.46	NHS Cost Collection (2024). SC41Z preparation for intensity modulated radiation therapy with technical support
One fraction of SABR	£239.83	NHS Cost Collection (2024). SC22Z deliver a fraction of treatment on a megavoltage machine
Radiofrequency ablation	£1,960.46	NHS Cost Collection (2024). YL02Z Standard Percutaneous Ablation of Lesion of Kidney

Resource	Unit cost	Source
Cryoablation	£3,474.14	NHS Cost Collection (2024). YL01Z Complex Percutaneous Ablation of Lesion of Kidney
Microwave ablation	£1,960.46	NHS Cost Collection (2024). YL02Z Standard Percutaneous Ablation of Lesion of Kidney
CT of one area, with contrast	£145.88	NHS Cost Collection (2024). RD22Z Computerised Tomography Scan of one area with pre- and post-contrast, 19 years and over
CT-CAP, with contrast	£123.03	NHS Cost Collection (2024). RD26z Computerised Tomography Scan of Three areas with contrast
MRI (abdominal) scan	£201.67	NHS Cost Collection (2024). RD02A Magnetic Resonance Imaging Scan of one area with post-contrast only, 19 years and over
MRI scan	£202.40	NHS Cost Collection (2024). RD05z Magnetic Resonance Imaging Scan of Two or Three areas with contrast
Ultrasound scan	£53.32	NHS Cost Collection (2024). RD41z Ultrasound Scan with duration of less than 20 minutes with contrast

SABR: stereotactic ablative radiotherapy, CT-CAP: computed tomography of chest, abdomen and pelvis, MRI: Magnetic resonance imaging.

1.1.11 Evidence statements

People with VHL: active surveillance

Two case series were identified for people with VHL who received active surveillance. These studies had a total of 27 participants and a median follow-up time of 76.1 months, where follow-up was either every 6 months or not reported. Both studies reported no distant recurrence. Both studies were judged to be of high risk of bias and directly applicable.

People with VHL: partial nephrectomy

Nine case series were identified for people with VHL who received partial nephrectomy. These studies had a total of 127 participants and a median follow-up time of 60 months, where follow-up ranged between 3- and 12-month intervals where reported.

- Overall mortality, cancer-specific mortality, and distant metastasis were reported in 4, 6, and 8 studies respectively. Three studies reported that participants had experienced distant metastasis (4% to 22% of participants had an event) and cancer-specific mortality (one study reported a CSS 10-year rate of 81% and 2 studies reported that 22% participants had cancer-specific mortality).

- Renal outcomes were reported in 7 studies: 4 studies reported no incidences of new onset CKD or need for dialysis or transplant, one study reported 7 incidences of new onset CKD (14% of participants had an event), and 2 studies reported need for dialysis or transplant (18% and 22% of participants had an event).

- All studies were judged to be at high risk of bias, and 7 studies were judged to be directly applicable, with 2 studies judged as partially applicable.

People with VHL: thermal ablation

Eight case series were identified for people with VHL who received thermal ablation. These studies had a total of 115 participants and a median follow-up time of 35.8 months, where final follow-up intervals 1- or 2- years post-treatment were between 6 and 12 months.

- Overall mortality, cancer-specific mortality, and distant metastasis were reported in 6, 5, and 5 studies respectively. Five studies reported occurrences of overall mortality (between 2% and 14% of participants had an event), and one study reported an incidence of distant metastasis and cancer-specific mortality (2% of participants had an event for both outcomes).
- Renal outcomes were reported in 6 studies, where only one study reported an incidence of need for dialysis or transplantation (10% of participants had an event).
- Four studies were judged to be of high and 4 of moderate risk of bias, and 6 studies were judged to be directly and 2 partially directly applicable.

People with VHL: SABR

One case study was identified for people with VHL who received SABR. This study had 7 participants and a median follow-up time of 43 months with follow-up frequency of 3 to 6 months.

- The study had a 2-year OS rate of 85.7% and a 2-year CSS rate of 100%.
- There were no events relating to relevant renal outcomes.
- The study was judged to be at low risk of bias and directly applicable.

People with VHL: radical nephrectomy

Three case series were identified for people with VHL who received radical nephrectomy. These studies had a total of 38 participants and a median follow-up time of 68 months, with follow-up intervals of at least yearly where reported.

- One of the studies reported 4 incidences of distant metastasis (21% of participants had an event), and two studies reported incidences of cancer-specific mortality (one study reported a 10-year rate for CSS of 36% and one study reported that 21% of participants had a cancer-specific mortality event).
- Renal outcomes were reported in 2 studies, where one reported incidences of new-onset CKD (50% of participants had an event) and one reported need for dialysis or transplantation (67% of participants had an event).
- All studies were judged to be at high risk of bias, and 2 were directly and one was partially directly applicable.

People with VHL: both radical nephrectomy and partial nephrectomy

Two case series were identified for people with VHL who received both radical nephrectomy and partial nephrectomy. These studies had a total of 5 participants and a median follow-up time of 79.5 months, where follow-up frequency was at least yearly where reported.

- Both studies reported overall mortality, cancer-specific mortality, and distant metastasis. One study reported that all participants experienced distant recurrence, and two participants experienced overall and cancer-specific mortality (50% of participants had an event for both outcomes).
- One study reported renal outcomes, where no participants had an event of need for dialysis or treatment.
- Both studies were judged to be at high risk of bias and were directly applicable.

People with BHDS: thermal ablation

Two studies were identified for people with BHDS who received thermal ablation. These studies had a total of 12 participants and a median follow-up time of 64 months, where follow-up was between 6 and 12 months 1-year post-treatment.

- Both studies reported mortality, distant recurrence and renal outcomes, however, no events were reported in either study.
- Both studies were judged to be of moderate risk of bias and were directly applicable.

People with HLRCC

One study (n=15) was identified for people with HLRCC. This study reported on 2 participants who received partial nephrectomy, 12 participants who received radical nephrectomy, and 1 participant who received both radical and partial nephrectomy. The median follow-up time was 34 months, and follow-up frequency was not reported.

- Overall mortality, cancer-specific mortality, and distant metastasis outcomes were reported. Overall mortality and cancer-specific mortality were only observed in the radical nephrectomy group, where 33% of participants had events, and distant metastasis was observed in the radical nephrectomy group, and for participants receiving both partial and radical nephrectomies (50% and 100% of participants experienced the event respectively).
- This study was judged to be of high risk of bias and directly applicable.

People with SDH-deficient RCC

One study (n=12) was identified for people with SDH-deficient RCC. This study reported on 5 participants who received partial nephrectomy, 5 participants who received radical nephrectomy, and 2 participants who received radical nephrectomy and contralateral wedge resection. The median follow-up time was 55 months, and follow-up frequency was not reported.

- Overall mortality, cancer-specific mortality, and distant metastasis outcomes were reported. Overall mortality and cancer-specific mortality were only observed in the partial nephrectomy group, where 20% of participants had events, and distant metastasis was observed in the radical nephrectomy and partial nephrectomy groups (20% of participants experienced the event in each group).

- This study was judged to be of high risk of bias and directly applicable.

Mixed hereditary RCC: partial nephrectomy

Three studies were identified for a mixed hereditary RCC population who received partial nephrectomy. These studies had a total of 137 participants and a median follow-up of 45 months, with yearly follow-up after 1-year post treatment where reported.

- All three studies reported on distant recurrence, and two of these studies had events of distant recurrence (3% and 4% of participants had an event). Three studies reported overall mortality/survival, where two study reported at least one death (one study reported 5-year OS rate of 93.3%, and one study reported that 2% of participants had an event of all-cause mortality). Two studies reported cancer-specific mortality/survival, where only one study reported at least one cancer-specific death (5-year OS rate of 96.7%).

- Both studies that reported on renal outcomes had events of need for dialysis or renal transplant (3% and 6% of participants had an event).

- All studies were judged to be at high risk of bias and partially directly applicable.

Mixed hereditary RCC: thermal ablation

Two studies were identified for a mixed hereditary RCC population who received thermal ablation. These studies had a total of 63 participants and a median follow-up time of 90 months, with yearly follow-up after 1-year post-treatment where reported.

- Both studies had one incidence of distant metastasis (2% and 10% of participants had an event), and there was one incidence of mortality in both studies (2% and 10% of participants had an event), with cancer-specific mortality only occurring in one study (where 2% of participants had an event).

- Only one study reported renal outcomes, where there was one event of new-onset CKD (10% of participants had an event).

- One study was judged to be of high risk of bias and partially direct, and one was judged to be at moderate risk of bias and directly applicable.

1.1.12 The committee's discussion and interpretation of the evidence

Referral of people with suspected heritable RCC predisposition syndrome who have RCC for genetic testing

An evidence review was not carried out to address the review question about factors that are associated with heritable RCC predisposition syndromes. The committee were aware that the UK national genomic test directory (NGTD) sets out clear criteria for when people should

receive genetic testing for mutations in genes associated with heritable RCC predisposition syndromes. (This is listed in the inherited cancer section of the rare and inherited disease eligibility criteria document.) The committee agreed that it was not necessary to conduct a review into the criteria for testing as the NGTD is reviewed regularly and kept up to date with new genes and revised criteria. Currently there are several gene panels relevant to people with suspected heritable RCC predisposition syndrome, including:

- R224 Inherited renal cancer [6 gene panel: BAP1, FH, FLCN, MET, SDHB, VHL]
- R225 Von Hippel Lindau syndrome [single gene test: VHL]
- R422 BAP1 associated tumour predisposition syndrome [single gene test BAP1]
- R363 Inherited predisposition to gastrointestinal stromal tumour (GIST) [6 gene panel: KIT, PDGFRA, SDHA, SDHB, SDHC, SDHD]
- R365 Fumarate hydratase-related tumour syndromes [single gene test FH]
- R228 Tuberous sclerosis [2 gene test: TSC1 and TSC2]

The committee therefore agreed to include a cross referral to the inherited cancer section of the rare and inherited disease eligibility criteria in a recommendation.

The committee discussed difficulties with using the NGTD criteria in practice that would generally apply to clinicians in urology, oncology, and primary care. These included having to check multiple criteria during a consultation with the person and knowing which criteria to check. They agreed that it would be beneficial to clinicians to have a list of key features that would lead them to suspect that a person could have a heritable RCC predisposition syndrome.

The committee drafted criteria based on the R224 panel in the NGTD and were mindful that criteria should be specific enough to be of use to clinicians but should also be broad enough so that they are still appropriate if there are changes to the criteria in the NGTD. In the recommendation the key features that would trigger a clinician to consult the detailed NGTD criteria if any criteria were present were: age at diagnosis; the presence of multiple renal lesions; family history of renal cancer; syndromic manifestations (signs or symptoms) consistent with a heritable RCC predisposition syndrome; and tumour subtype commonly associated with heritable RCC predisposition syndrome. The committee noted that clinicians would require more specific guidance around the criterion of age at diagnosis. Therefore, the criterion for age references the current age for eligibility for the R224 panel (up to age 46 inclusive) or an age eligible for inherited renal cancer genetic testing based on the rare and inherited disease eligibility criteria in the NGTD to ensure that the recommendation remains relevant for other genetic tests, and to future-proof the recommendation if the age criteria in the NGTD change.

The committee confirmed that most tests are currently carried out in clinical genetics, however, some testing is requested by oncology departments. The committee noted that there is a move towards mainstreaming where various specialities can request genetic testing. In addition, many clinicians have access to local policies that list criteria to determine when they should refer people for genetic testing for heritable RCC predisposition syndromes, but here is variation in practice.

The committee recognised that local policies and procedures as well as the NGTD determine who can request testing directly. They therefore made a separate recommendation for people who can request testing directly. The committee agreed that if any of the criteria associated with having a heritable RCC predisposition syndrome in their recommendation

applied, then the clinician should consult the rare and inherited disease eligibility criteria for inherited renal cancer in the NGTD for more details, and to access the most up to date criteria. They noted that the criteria may change in the future, and new criteria and gene panels may be added. Using the NGTD criteria would also enable them to determine which gene panel(s) to request. If the person met any of the criteria in the NGTD for having a heritable RCC predisposition syndrome, then the clinician should request any relevant tests.

The committee agreed that not all clinicians are able to request testing directly, and in some cases local policies and procedures may state that clinicians should refer people with a suspected heritable RCC predisposition syndrome for a detailed assessment and potential testing. In these cases, the clinician should assess the person against the criteria associated with having a heritable RCC predisposition syndrome listed in the recommendation, and if the person meets any of the criteria, they should refer them to a relevant healthcare professional. They made a recommendation to reflect this.

As part of evidence review D on information needs, the committee made recommendations about the information to be provided before testing, and after diagnosis, to people who are undergoing genetic testing to determine whether they have a heritable RCC predisposition syndrome. See the committee discussion of the evidence review D for more information about how these recommendations were drafted.

The committee highlighted that once people who have a RCC have been diagnosed with a heritable RCC predisposition syndrome, they should be referred to a specialist MDT with expertise in managing renal lesions in this population. These people would also need specialist management of non-RCC manifestations of the syndrome, which may involve other specialities.

1.1.12.1. The outcomes that matter most for management of RCC in people with a heritable RCC predisposition syndrome

An evidence review was carried out to address the review question looking at the management of RCC in people with a heritable RCC predisposition syndrome. The committee noted that people with a hereditary RCC predisposition syndrome are likely to have multiple RCCs in their lifetime, and therefore treatment needs to balance oncological outcomes with preserving renal function. Therefore, the committee agreed that the most important outcomes are the survival outcomes, the adverse renal outcomes of new onset chronic kidney disease and need for dialysis or renal transplantation. The committee agreed that preserving renal function is important as people receiving dialysis have poorer quality of life and it is not always possible for people to receive a renal transplant. Quality of life was also an important outcome, but no evidence was identified for this.

The committee chose not to include the outcomes of local recurrence and incidence of new primary cancers in the protocol, as this population would be expected to develop future RCCs and so management that prioritises sparing renal tissue is more important than preventing development of subsequent lesions.

1.1.12.2 Certainty in the evidence

Comparative evidence was not identified for this review, and all the evidence came from case series, meaning that it was not possible to carry out GRADE, and risk of bias and applicability were presented separately. There was a total of 26 case series: 17 studies were

in people with VHL, 2 studies were in people with BHD, 1 study was in people with HLRCC, 1 study was in people with SDH-deficient RCC, and 5 studies were in a mixed population of heritable RCC predisposition syndromes. Only evidence relating to interventions was identified, and there was no evidence relating to follow-up strategies.

Nineteen studies were assessed as being at high risk of bias, 6 at moderate and 1 at low risk of bias, with main reasons for downgrading being the retrospective study design, and poor reporting of the study population, eligibility criteria, and funding. Eighteen studies were judged as being directly applicable, and 8 studies were judged as being partially applicable due to either lack of information around whether participants had confirmed heritable RCC predisposition syndrome, and mixed heritable RCC predisposition syndrome populations.

There were several key limitations of the evidence: these included the case series study design, high risk of bias, and that all the studies had few participants (n=5 to 58). Crucially, the committee highlighted that study participants were likely assigned to treatment based on their disease status, and therefore it was likely that outcomes were not primarily attributable to the intervention that they received. For example, partial nephrectomy is the treatment of choice for localised RCCs in people with VHL, and so participants who received total nephrectomy likely had disease characteristics that prompted more radical treatment. The committee also noted that there is a high likelihood of reporting bias in these studies, and it is not possible to tell from the evidence the impact of partial nephrectomy on survival and adverse renal outcomes. The committee agreed that the case series study design meant that the evidence was of insufficient quality to be useful for recommendation drafting but could inform discussion. Therefore, recommendations would be made by consensus and informed by the experience and expertise of the committee. For this reason, associated recommendations would be weak recommendations. The committee highlighted that large real-world evidence studies would be beneficial for informing future recommendations, but they agreed not to draft a research recommendation, as this type of study could not feasibly provide useful information to inform management due to the low number of people with heritable RCC predisposition syndromes.

No evidence was identified for the following heritable RC subtypes: BAP1 tumour predisposition syndrome (BAP1-TPDS), hereditary papillary renal carcinoma (HPRC), hereditary paraganglioma/ pheochromocytoma (PGL/PCC), and tuberous sclerosis complex (TSC).

1.1.12.3 Benefits and harms

Overview of the management of people with a heritable RCC predisposition syndrome

The committee discussed the management of people with a heritable RCC predisposition syndrome using their experience and expertise. They noted that people diagnosed with a heritable RCC predisposition syndrome undergo regular surveillance for lesions (renal and non-renal) associated with their condition. The committee discussed that in their experience, this surveillance is usually co-ordinated by a clinical genetics team, however, this can vary depending on the treating centre. This type of surveillance is out of scope for the guideline, as it is being carried out on people who may not yet have a suspected RCC.

When renal lesions are identified, people are referred to a specialist urology MDT with expertise in managing renal masses in people with heritable RCC predisposition syndromes. At this point, they may undergo active surveillance for localised RCC to specifically monitor

the lesion or have active treatment. If active surveillance is undertaken, people will receive regular imaging until active treatment is appropriate. Following active treatment, people receive follow-up imaging before being discharged back to the clinical genetics team. However, people with a heritable RCC predisposition syndrome and RCC often have multiple renal lesions at different stages of active surveillance, treatment and follow up.

It is also possible for people with an undiagnosed heritable RCC predisposition syndrome to enter the heritable RCC predisposition syndrome treatment pathway after identification of a suspicious lesion and subsequent diagnosis of a relevant syndrome. In this population, the committee noted that at first presentation a lesion may be biopsied prior to surgery. However, when people do not have a biopsy, the histological subtype is unknown until after treatment, at which point people with tumour histology subtype indicating a heritable RCC predisposition syndrome will be referred for genetic testing. The committee also noted that it is common for people in this population to have many lesions upon first presentation.

People with heritable RCC predisposition syndromes are likely to have multiple RCCs over their lifetime, and the committee noted that treatment aims to balance the risk of developing metastases with preserving renal function for as long as possible. Therefore, management options such as active surveillance are used frequently until the lesions reach a size where other interventions (such as surgery) are required.

Management of people with von Hippel-Lindau syndrome and other less aggressive heritable RCC predisposition syndromes

Active surveillance for localised RCC

The evidence from 2 studies with a total of 27 participants showed that when people with von Hippel-Lindau syndrome (VHL) and small RCCs had active surveillance until the RCC reached a threshold of 3 to 4cm, they did not experience any distant metastases. The committee agreed that this finding was consistent with their clinical experience, and that it is very rare for an RCC to metastasise below 3cm. The committee noted that it is usual practice to carry out active surveillance in this population until the lesion reaches 3cm, and that although the threshold is smaller for this population than recommended for the sporadic population (4cm), it balances the need to prevent metastasis with the need to preserve renal tissue for as long as possible. They therefore drafted a recommendation for active surveillance for any renal lesions that are less than 3 cm in diameter in people with a heritable RCC predisposition syndrome that is not associated with more aggressive RCC.

The committee noted that it is important that people with a heritable RCC predisposition syndrome have imaging during active surveillance using MRI or ultrasound and made a recommendation to reflect this. This is because people with heritable RCC predisposition syndrome require regular imaging throughout their lifetime, and use of CT imaging would result in high exposure to radiation in the long term and increase their risk of developing other tumours. This consideration also applies to other imaging they might have during follow up of RCC after treatment, or for routine surveillance to detect new renal or other types of lesions. This recommendation is consistent with guidance from the UK Cancer Genetics Group, who recommend MRI or ultrasound for routine surveillance of VHL, Hereditary papillary renal carcinoma (HPRC), Birt-Hogg-Dubé syndrome (BHD), BAP1 tumour predisposition Syndrome (BAP-1-TPDS), and Hereditary leiomyomatosis and renal cell cancer (HLRCC).

The committee agreed that the active surveillance schedule would be determined by lesion characteristics and made a consensus recommendation for a minimum schedule that could

be used for people with a renal lesion and a heritable RCC predisposition syndrome that is not associated with more aggressive RCC. They agreed that from the start of active surveillance, imaging should take place between 3 and 6 months, and then at 12 months for the first year. This is consistent with active surveillance of RCC that is not associated with a heritable RCC predisposition syndrome (sporadic RCC). For year 2 onwards they recommended that imaging should happen at least every year. In both cases they agreed that this schedule should be adapted by the specialist MDT if there are characteristics or changes in the lesion(s) indicating more frequent or additional imaging is needed.

Similar to people undergoing active surveillance for RCC that is not associated with a heritable RCC predisposition syndrome (sporadic RCC), the committee recommended that people with a RCC associated with heritable RCC predisposition syndrome who are undergoing active surveillance should have a written care plan. This is expected to include details of a designated healthcare professional who can be the point of contact if, for example, the person experiences persistent symptoms that concern them. The components of this plan are the same as for people with sporadic RCC (see evidence review E on active surveillance for more details) and include information about cancer care reviews in primary care as well as the details of the imaging schedule.

The committee discussed moving from active surveillance to treatment. They agreed that progression to treatment from active surveillance should be primarily driven by lesion size (if the lesion is 3 cm or larger) rather than growth rate in this population, but that it can be important to take growth rate into account if it suggests that the lesion size threshold might be reached before the next scan. The committee also stressed that another reason to move to active treatment would be if this is requested by the person with RCC who has a hereditary RCC predisposition syndrome, but that these people may have competing clinical priorities that impact when they are able to move to treatment and what treatment is suitable for them. Their recommendation reflects these points.

Nephron sparing interventions and radical treatments

The committee agreed that in their clinical experience, some people with RCC who have a heritable RCC predisposition syndrome may prefer to have sub-3 cm renal lesions removed instead of undergoing active surveillance, due to concerns that removing the lesion when it has grown will result in more loss of healthy renal tissue. While the committee agreed that this is a reasonable concern, they noted that there is no evidence to support the approach of removing sub-3 cm lesions and reiterated the importance of counselling patients and providing appropriate information to help them with decision making.

The committee noted that historically, people with RCC who had heritable RCC predisposition syndrome were treated with bilateral total nephrectomy for multiple bilateral lesions, and that while cancer-specific mortality was low, quality of life for this population was severely reduced as they needed life-long dialysis unless they were able to have a renal transplant. The committee highlighted that there is now more of an emphasis on preserving renal function for as long as possible. Therefore, partial nephrectomy is preferred over total nephrectomy regardless of the increased risk of complications associated with partial nephrectomy for people with less aggressive heritable RCC predisposition syndromes in situations where this surgery can completely remove or destroy the renal lesion based on the lesion’s location and size, and the individual’s clinical characteristics. The committee used their experience and expertise to draft a recommendation to reflect this.

The committee confirmed that thermal ablation is also a good option for people with VHL (or other less aggressive heritable RCC predisposition syndromes) for whom partial

nephrectomy is unsuitable. They noted that stereotactic ablative radiotherapy (SABR) could be an option for these people (as it is for people with sporadic RCC), although there is less evidence for the use of SABR in people with RCC in general than there is for thermal ablation. However, they agreed that partial nephrectomy should ideally be performed before thermal ablation or SABR as these treatments can cause inflammation and potentially scarring of both the treated kidney and normal surrounding structures such as the bowel, which can increase the risk of complications of any subsequent surgery. They therefore made a recommendation to consider using thermal ablation or SABR as other potential nephron-sparing treatment options if they can completely destroy the lesion **and** partial nephrectomy is not possible or is likely to be very challenging due to previous partial nephrectomy.

While the level of radiation from one cycle of treatment with SABR would unlikely be high enough to cause radiation-induced lesions, the committee noted that a second course of SABR to a nearby site would likely exceed the dose constraints for the normal kidney and nearby structures such as bowel, putting the patient at too high a risk of late radiation induced toxicity.

The committee were also aware of NICE's technology appraisal on Belzutifan for treating tumours associated with von Hippel-Lindau disease [TA1011], which recommends treatment for VHL-associated RCCs when localised procedures are unsuitable or undesirable, and noted that this would be incorporated into the guideline.

Management of people with a heritable syndrome associated with more aggressive RCC such as Hereditary leiomyomatosis and renal cell cancer (HLRCC)

There was also very limited evidence in people with Hereditary leiomyomatosis and renal cell cancer (HLRCC) (1 study, n=15), and most of the participants in this study received total nephrectomy. High mortality and high metastasis were observed in this study, and the committee highlighted that this was in line with their clinical experience, as RCC in people with HLRCC is associated with aggressive disease. The committee noted that RCC can metastasise at sub-centimetre lesion sizes in HLRCC and agreed that total nephrectomy or excision with wider margins is more appropriate for this population than active surveillance due to the aggressive nature of the disease. However, the committee noted that there may be competing needs related to comorbidities, and therefore immediate treatment may not always be possible. In these cases, it may be appropriate to use active surveillance to monitor the RCC until radical treatment is possible. However, they agreed that in the rare cases where active surveillance is used for people with a heritable syndrome associated with more aggressive RCC the active surveillance schedule needs to be determined on an individual basis taking into account the person's clinical needs and that this should be more frequent than the one suggested for people with syndromes associated with less aggressive RCC. The committee used their experience and expertise to make recommendations to reflect these points. The committee also made a recommendation to consider total nephrectomy or surgically removing more tissue around the lesion during partial nephrectomy for people with syndromes associated with more aggressive RCC.

Limited evidence was identified for succinate dehydrogenase deficient renal cell carcinoma (SDH-deficient RCC) syndromes (1 study, n=12), where most people received either total nephrectomy or partial nephrectomy. The committee discussed that although low-grade SDH-deficient RCCs tend to be fairly indolent, lesions can be aggressive when high-grade

features are seen histologically. Due to this aggressive nature the committee agreed that they would manage it in the same way as HLRCC.

No evidence was identified for BAP1-TPDS, and the committee discussed that while BAP1-TPDS may be associated with aggressive RCC, the syndrome is extremely rare.

Management of people with other subtypes of heritable RCC predisposition syndrome

As for VHL, evidence for Birt-Hogg-Dubé syndrome (BHD) was limited to case series and there was no evidence for other types of heritable RCC predisposition syndromes. As a result, the committee used their clinical experience and agreed that most subtypes should be treated according to the management recommendations for VHL, with exception of syndromes associated with aggressive RCC, where the same management as HLRCC should be followed.

Follow-up after treatment for people with any heritable RCC predisposition syndrome

No evidence was identified for studies assessing different follow-up strategies for people with heritable RCC predisposition syndrome after treatment for localised or locally advanced RCC. Therefore, the committee relied on their clinical experience in the drafting of recommendations and adapted the recommendations on follow up for people with sporadic RCC (see evidence review F on follow up of previously treated renal cell carcinoma). The committee agreed that follow-up imaging for people with heritable RCC predisposition syndrome should not be less frequent than that for standard surveillance as recommended by the UK Cancer Genetics group. (In this context standard surveillance refers to regular surveillance protocols for people with a known heritable RCC predisposition syndrome to ensure early diagnosis and timely treatment of renal cancer or other signs and symptoms associated with the syndrome.) This standard surveillance is annually for VHL, BHD, BAP-1-TPDS, and HLRCC, and every 2 years for HPRC. Consequently, the committee agreed that the intermediate follow-up schedule they previously recommended in review F for people with sporadic RCC should be used as a minimum (imaging at 6- and 12-months post-treatment, and then annually). The committee highlighted that follow-up imaging would be in addition to standard surveillance for non-renal lesions and could also be in addition to active surveillance for other renal lesions. They agreed that similar to people with sporadic RCC where CT should be avoided to reduce radiation exposure, MRI of the abdomen and CT of the chest should be considered during follow up for people with RCC who have a heritable RCC predisposition syndrome. They drafted recommendations to reflect these points.

The recommendation for information to provide during follow up is very similar to the one for information during active surveillance and is based on the corresponding recommendation for people with sporadic RCC with the addition of a statement about co-ordinating imaging schedules where possible (see below for more discussion about this point).

The committee noted that similar to sporadic RCC, there is no evidence to determine when follow up imaging should finish for people with a heritable RCC predisposition syndrome who have been treated for RCC. However, there is a key difference in that they are not discharged completely but rather continue to receive standard surveillance as organised by the clinical genetics team for their syndrome. The committee used their experience and expertise to recommend that after 5 years of follow up there should be a discussion with the team that manages the standard surveillance about when to stop follow up for a treated RCC

and return solely to standard surveillance. The committee noted that in practice follow up and standard surveillance may overlap (although a person would not have a scan for surveillance if they just had a scan for follow up) and that decision when to stop follow up would be based on the individual's clinical needs. They also noted that there are additional complexities in that the person may have other RCC that are being monitored by active surveillance or that are being treated at the same time.

1.1.12.4 Cost effectiveness and resource use

No published economic evidence was identified, and original economic modelling was not conducted for the review question on the management of hereditary renal cell carcinoma. Evidence was not searched for the question on risk factors are associated with hereditary RCC, as the National genomic test directory for rare and inherited diseases was cross referred to instead.

The recommendation listing the factors to assess before doing a detailed assessment following the NGTD may help standardise the early stage of the genetic assessment process but is not expected to have a large resource impact, as the numbers of people being assessed are likely to be relatively small.

The recommendations made on the management of heritable predisposition syndromes for RCC are broadly aligned with current clinical practice and are not expected to have a substantial resource impact but encourage standardisation of practice.

When making their recommendations, the committee considered the importance of the balance between preventing metastases and maintaining kidney function, given the population with heritable predisposition syndromes for RCC are likely to be younger than the general population with RCC and may get multiple lesions in their lifetimes. Management for more advanced RCC is likely to incur significant costs and quality of life detriments, but similarly, more aggressive management of RCC with nephrectomy may require management of complications of reduced renal function, for example dialysis, which are also associated with substantial lifetime costs and quality of life decline. The recommendations made on management of RCC in this heritable predisposition syndrome population therefore reflect the need to preserve renal function whilst managing the RCC and the committee considered that they are broadly aligned with current clinical practice.

The committee noted that people with heritable predisposition syndromes for RCC frequently have other indications alongside their RCC that require monitoring, and recommended that any monitoring, active surveillance, and follow up for their RCC should be coordinated with any other imaging they may be having to avoid duplication. This would avoid wasting resources and is beneficial to the patient in terms of reducing unnecessary travel to additional appointments.

1.1.12.5 Other factors the committee took into account

The committee also made recommendations about biopsy for people with RCC who have a heritable RCC predisposition syndrome as part of review J (see review J on renal biopsy for more details).

Equality considerations

People with heritable RCC predisposition syndrome are likely to have RCC at a younger age, and younger adults may face additional costs associated with attending appointments if they have to pay for childcare.

The burden of imaging is high for people with heritable RCC disposition syndromes, as they require general surveillance for non-renal lesions associated with the heritable RCC syndrome in addition to imaging of the RCC. They may also have multiple RCCs in different stages of active surveillance, monitoring treatment effects or follow up. This burden may be exacerbated by the need to travel longer distances for appointments in the specialist centres that are capable of managing their complex needs. The committee were aware that it can be difficult for people to manage repeated imaging while juggling work and family demands and can result in missed appointments and fatigue. This may be particularly hard if people have disabilities that affect their mobility and/ or need to be accompanied by family members or carers for support.

The committee were clear that it is important for services to co-ordinate imaging by scheduling scans on the same day where possible to lessen this burden for people with heritable RCC predisposition syndromes. This may also have the benefit of reducing unnecessary duplication of imaging and free up some imaging capacity, which is known to be a limited resource in many areas of the country. They therefore recommended co-ordination of imaging within the urology MDT in cases where the person has multiple renal lesions at different stages of management (including active surveillance) or follow up, and with the other specialities involved in managing the syndrome (for example endocrinology for VHL and respiratory for BHD). The committee also highlighted that many people with heritable RCC predisposition syndromes value remote appointments over face-to-face appointments where possible (such as when results of imaging are being shared) as this allows them to fit in appointments around everyday life.

The committee noted that people who are adopted or have no knowledge of their family background may be disadvantaged during an assessment for a heritable RCC predisposition syndrome as they would be unaware of any family history of renal cancer, which is a criterion for when to suspect a heritable RCC predisposition syndrome.

The committee also noted that SMARCB1-deficient renal medullary carcinoma (medullary RCC) is more common in young black men with sickle cell traits, and this is a particularly aggressive form of disease. However, the committee agreed while this is still recorded in the EHIA for the guideline, this is not strictly related to a heritable RCC predisposition syndrome and so is not relevant to this review.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.16.1 to 1.16.3, 1.16.5, 1.17.1 to 1.17.7, 1.18.1 to 1.18.3, 1.20.1 to 1.20.5.

1.1.14 References – included studies

1.1.14.1 Effectiveness

Allasia, Marco, Soria, Francesco, Battaglia, Antonino et al. (2017) Radiofrequency Ablation for Renal Cancer in Von Hippel-Lindau Syndrome Patients: A Prospective Cohort Analysis. Clinical genitourinary cancer

Bodard, Sylvain, Boudhabhay, Idris, Dariane, Charles et al. (2022) Percutaneous Thermal Ablation for Renal Tumors in Patients with Birt-Hogg-Dube Syndrome. Cancers 14(20)

Bratslavsky, Gennady, Liu, Jack J, Johnson, Aaron D et al. (2008) Salvage partial nephrectomy for hereditary renal cancer: feasibility and outcomes. The Journal of urology 179(1): 67-70

Chan, Vinson Wai-Shun, Lenton, James, Smith, Jonathan et al. (2022) Multimodal image-guided ablation on management of renal cancer in Von-Hippel-Lindau syndrome patients from 2004 to 2021 at a specialist centre: A longitudinal observational study. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 48(3): 672-679

Drachenberg, Darrel E, Mena, Othon J, Choyke, Peter L et al. (2004) Parenchymal sparing surgery for central renal tumors in patients with hereditary renal cancers. The Journal of urology 172(1): 49-53

Frydenberg, M; Malek, R S; Zincke, H (1993) Conservative renal surgery for renal cell carcinoma in von Hippel-Lindau's disease. The Journal of urology 149(3): 461-4

Gaillard, Victor, Tricard, Thibault, Garnon, Julien et al. (2020) Repeat ablative therapy in hereditary or multifocal renal cancer: Functional and oncological outcomes. Urologic oncology 38(10): 797e15-797e20

Gill AJ, Hes O, Papathomas T et al. (2014) Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. The American journal of surgical pathology 38(12): 1588-1602

Grubb, Robert L 3rd, Franks, Michael E, Toro, Jorge et al. (2007) Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer. The Journal of urology 177(6): 2074-80

Gupta, Gopal N, Peterson, James, Thakore, Kailash N et al. (2010) Oncological outcomes of partial nephrectomy for multifocal renal cell carcinoma greater than 4 cm. The Journal of urology 184(1): 59-63

Hes, F J, Slootweg, P J, van Vroonhoven, T J et al. (1999) Management of renal cell carcinoma in von Hippel-Lindau disease. European journal of clinical investigation 29(1): 68-75

Iwamoto, Yoichi, Kanda, Hideki, Yamakado, Koichiro et al. (2011) Management of renal tumors in Von Hippel-Lindau disease by percutaneous CT fluoroscopic guided radiofrequency ablation: preliminary results. Familial cancer 10(3): 529-34

Johnson, Aaron, Sudarshan, Sunil, Liu, Jack et al. (2008) Feasibility and outcomes of repeat partial nephrectomy. The Journal of urology 180(1): 89-93

Kirste, Simon, Ruhle, Alexander, Zschiedrich, Stefan et al. (2022) Stereotactic Body Radiotherapy for Renal Cell Carcinoma in Patients with Von Hippel-Lindau Disease-Results of a Prospective Trial. Cancers 14(20)

Lund, G O, Fallon, B, Curtis, M A et al. (1994) Conservative surgical therapy of localized renal cell carcinoma in von Hippel-Lindau disease. Cancer 74(9): 2541-5

Matsui, Y, Hiraki, T, Gobara, H et al. (2019) Percutaneous thermal ablation for renal cell carcinoma in patients with Birt-Hogg-Dube syndrome. Diagnostic and interventional imaging 100(11): 671-677

Matsukawa, A., Yanagisawa, T., Shimizu, K. et al. (2024) Percutaneous cryoablation of renal cell carcinomas in patients with Von Hippel-Lindau disease: Functional and oncological outcomes. International Journal of Urology 31(4): 448

Novick, A C and Streem, S B (1992) Long-term followup after nephron sparing surgery for renal cell carcinoma in von Hippel-Lindau disease. The Journal of urology 147(6): 1488-90

Osman, F.H., Chan, V.W.-S., Breen, D.J. et al. (2023) Oncological and Peri-Operative Outcomes of Percutaneous Cryoablation of Renal Cell Carcinoma for Patients with Hereditary RCC Diseases-An Analysis of European Multi-Centre Prospective EuRECA Registry. Cancers 15(13): 3322

Park, Byung Kwan and Kim, Chan Kyo (2010) Percutaneous radio frequency ablation of renal tumors in patients with von Hippel-Lindau disease: preliminary results. The Journal of urology 183(5): 1703-7

Ploussard, Guillaume, Droupy, Stephane, Ferlicot, Sophie et al. (2007) Local recurrence after nephron-sparing surgery in von Hippel-Lindau disease. Urology 70(3): 435-9

Schuhmacher, Patrick, Kim, Emily, Hahn, Felix et al. (2019) Growth characteristics and therapeutic decision markers in von Hippel-Lindau disease patients with renal cell carcinoma. Orphanet journal of rare diseases 14(1): 235

Shinohara, N, Nonomura, K, Harabayashi, T et al. (1995) Nephron sparing surgery for renal cell carcinoma in von Hippel-Lindau disease. The Journal of urology 154(6): 2016-9

Steinbach, F, Novick, A C, Zincke, H et al. (1995) Treatment of renal cell carcinoma in von Hippel-Lindau disease: a multicenter study. The Journal of urology 153(6): 1812-6

Wessendorf, Joel, Konig, Alexander, Heers, Hendrik et al. (2021) Repeat Percutaneous Radiofrequency Ablation of T1 Renal Cell Carcinomas is Safe in Patients with Von Hippel-Lindau Disease. Cardiovascular and interventional radiology 44(12): 2022-2025

Yang, Bo, Autorino, Riccardo, Remer, Erick M et al. (2013) Probe ablation as salvage therapy for renal tumors in von Hippel-Lindau patients: the Cleveland Clinic experience with 3 years follow-up. Urologic oncology 31(5): 686-92

1.1.14.2 Economic

No economic evidence was identified for this review.

1.1.15 References – other

Camp C, O'Hara J, Hughes D, Adshead J. Short-term Outcomes and Costs Following Partial Nephrectomy in England: A Population-based Study. 2018. European urology focus, 4(4) 579-585

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

Effectiveness review protocol for management and follow-up strategies for adults with heritable renal cell carcinoma (RCC)

ID	Field	Content
1.	Review title	Management and follow-up strategies for adults with heritable renal cell carcinoma (RCC)
2.	Review question	What is the clinical and cost effectiveness of: • different interventions (surgical or non-surgical) or active surveillance, compared to each other and • different follow up strategies compared to each other for adults with heritable renal cell carcinoma?
3.	Objective	To evaluate management and follow-up plans for adults with heritable RCC
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL For the economics review the following databases will be searched: • Embase • MEDLINE ALL • Econlit • INAHTA Database functionality will be used, where available, to exclude: • Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters • Records from clinical trial registries • 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/ OECD countries. The information services team at NICE will quality assure the principal search strategy. Any revisions or additional steps will be agreed by the review team before being implemented. The full search strategies for all databases will be published in the final review.

5.	Condition or domain being studied	Heritable renal cell carcinoma
6.	Population	Adults with heritable renal cancer susceptibility syndromes and: • Suspicious renal lesions on imaging or • Confirmed RCC through biopsy or surgical pathology RCC is confirmed according to the clinical or pathological TNM staging and WHO subtyping classification. Heritable renal cancer susceptibility syndromes are confirmed by genetic testing. We will include populations who have or have not had previous focal treatments (nephrectomy or thermal ablation [cryotherapy, radiofrequency ablation, microwave ablation]). Exclusions: People with metastatic RCC

7.	Intervention	**Non-pharmacological treatments:**
		
		• Active surveillance or delayed interventions
		
		• Nephron-sparing treatments:
		  ○ partial nephrectomy
		  ○ thermal ablation
		  ○ SABR
		
		• Radical (total) nephrectomy
		
		Pharmacological treatments:
		TA incorporation only.
		We will incorporate relevant NICE TA recommendations in the guideline from NICE TA ID3932 Belzutifan for treating tumours associated with von Hippel-Lindau disease when this is published.
		
		Follow-up strategies:
		• Any follow-up strategies

8.	Comparator	• Different non-pharmacological management approaches for hereditary RCC compared with each other • Different follow-up approaches compared with each other • No comparison (where no comparative evidence is identified)
9.	Types of study to be included	We will preferentially include systematic reviews of RCTs and primary RCTs. If RCTs are not available, systematic reviews of observational studies and primary observational studies (including cohort and

		case series) will be considered. Where there are large numbers of non-randomised controlled or comparative observational studies, studies will only be included if they adjust for a minimum of the following confounding factors: [age, renal function at baseline and heritable RC predisposition syndrome]. Adjustment must use one of the methods stated in NICE TSD 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal. Where insufficient evidence has been identified that adjusts for confounders, we will include studies that have not been adjusted for all confounders but will downgrade them for risk of bias using the ROBINS-I tool. Where no comparative evidence is identified, we will include non-comparative evidence (case series).
10.	Other exclusion criteria	• Abstracts, conference presentations and theses • Non-human studies • Non-English language studies • Case studies
11.	Context	There is currently no national guideline in the UK on the diagnosis and treatment of kidney cancer and audit data indicates variation in the clinical practice within NHS. Stakeholders identified this gap and NICE was commissioned to develop a guideline on kidney cancer by NHSE. Some individuals with RCC may have a heritable mutation in a gene known to lead to a predisposition to RCC. The criteria for germline testing have been described in the National genomic test directory for rare and inherited diseases. For adults with a new diagnosis of a renal cancer, a diagnosis of a heritable predisposition to developing RCC may be relevant to their kidney cancer management plan. This review aims to evaluate management and follow-up plans for adults with a confirmed heritable cancer predisposition syndrome who have or have had RCC.
12.	Outcomes	**Survival outcomes:** • Overall survival (time to event data) • Cancer-specific survival (time to event data) • Metastasis-free survival (time to event data) **Recurrence outcomes:** This outcome will only be considered if no data on metastases-free survival is available. • Distant recurrence (dichotomous data; latest time point) **Adverse events/long term consequences:**

		• New onset chronic kidney disease (stages 3a to 5; dichotomous data; latest time point) • Need for dialysis or renal transplant (dichotomous data; latest time point) **Quality of life outcomes:** • EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30) (dichotomous or continuous data) • EuroQol-5 dimensions (EQ-5D; dichotomous or continuous data)
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 6.4).
14.	Risk of bias (quality) assessment	The risk of bias for will be assessed as follows: • RCTs will be assessed using the Cochrane Risk of Bias v.2.0 checklist • for systematic reviews, the Risk of Bias in Systematic Reviews (ROBIS) tool will be used. • Comparative observational and non-RCT studies will be assessed using the Cochrane Risk of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool. • case series will be assessed using the institute of Health Economics (IHE) checklist for case series studies. Use of these tools is described in Developing NICE guidelines: the manual
15.	Strategy for data synthesis	Where possible, meta-analyses will be conducted to combine study results. Pairwise meta-analyses will be performed in Cochrane Reman Web. Continuous outcomes will be analysed as pooled mean differences (using the inverse variance method). Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Hazard ratios will be pooled using the generic inverse-variance method. Pooled data will be analysed with a fixed-effects model and inspected for heterogeneity. Where there is substantial statistical heterogeneity (defined as I^2 above 50%), a random-effects model will be used to pool the data. Where data can be disambiguated it will be separated into the subgroups identified in section 16.

		GRADE will be used to assess the quality of the outcomes. Data from randomised controlled trials, comparative observational studies, and non-randomised comparative trials will be initially rated as high quality and will be downgraded from this point. To assess imprecision, where there are no defined MIDs in the published literature, we will set the MID as the line of no effect for all outcomes (1.0 for dichotomous outcomes and 0 for continuous outcomes). The second decision threshold will be a sample size of 200.
16.	Analysis of sub-groups	Where data allows, analyses will be stratified by type of management received. Where the data allows, subgroup analyses may be conducted to explore heterogeneity considering the following: • genetic mutation subtypes • Aggressive tumours vs slow-growing tumours • tumour size
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	February 2025
21.	Anticipated completion date	March 2026
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: • Sarah Boyce, Senior technical analyst • Sarah Matthews, Technical analyst • Lindsay Claxton, Health economics adviser • Hannah Tebbs, Senior health economist • Yuanyuan Zhang, Senior 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	Renal cell carcinoma, genetic assessment, active surveillance
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 19: Economic review protocol

ID	Field	Content
1.	Review title	What is the clinical and cost effectiveness of: • different interventions (surgical or non-surgical) or active surveillance, compared to each other and • different follow up strategies compared to each other for adults with heritable renal cell carcinoma?
2.	Objective	To identify economic studies for management and follow-up plans for adults with heritable renal cell carcinoma
3.	Inclusion criteria	• Populations, interventions and comparators as specified in the effectiveness review protocol. • Relevant comparative economic study design: cost–utility analysis • Decision analytic model-based or within-trial economic analyses • OECD countries (except USA) • Healthcare and personal social services cost perspective • Studies published from 2010 – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs High-quality studies in line with the NICE reference case (recent UK NHS/PSS cost-utility analyses using the QALY as the measure of outcome) are the most applicable to NICE decision making. Not all studies meeting the inclusion criteria will therefore necessarily be used in decision-making - see Review strategy below for details.
4.	Exclusion criteria	• Conference posters or abstract only studies – these do not provide sufficient information for quality assessment. • Studies published before 2010 – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs • Studies from non-OECD countries or the USA – these are considered unlikely to be applicable to the UK NHS setting due to substantial differences in healthcare delivery and unit costs. • Non-comparative economic analyses including cost-of-illness studies. • Letters, editorials or commentaries, study protocols or reviews of economic evaluations (recent reviews will be ordered and the bibliographies will be checked for relevant individual economic studies, which will then be ordered and checked for eligibility). • Non-English language papers. • Studies considering exclusively intervention costs, e.g. medicine acquisition costs, without considering wider healthcare costs associated with the management of renal cell carcinoma. • Studies comparing costs of branded vs generic forms of the same medicine. • Studies only focussing on productivity losses or gains.

5.	Search strategy	An economic study search will be undertaken covering review questions relating to the management and follow up of heritable renal cell carcinoma, using guideline population-specific terms and a health economic study filter. For search details see appendix B below. The following databases will be searched: • MEDLINE All, Ovid • Embase, Ovid • International HTA database, International Network of Agencies for Health Technology Assessment (INAHTA) • Econlit
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

A list of hereditary terms were identified by the clinical teams consulting with a geneticist. Additional terms were also gathered from the NCCN version 3.2024 hereditary renal cell carcinoma guideline.

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

OECD:

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.

Observational filter:

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

Systematic reviews filters:

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

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

RCT 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.

Cost effectiveness searches

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

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

Health state utility balanced filter was used without modification:

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

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

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

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

Key decisions

The population has been limited to hereditary (using both broad and specific terms) types of kidney cancer. The intervention terms used were based on the terms used in the single search strategy for reviews A, B, C, H1 and H2 combined (review A: surgical interventions for localised RCC, review B: non-surgical interventions for localised RCC, review C: nephrectomy or stereotactic ablative radiotherapy for locally advanced RCC, reviews H1 and H2: non-pharmacological management of advanced RCC).

One study (Gill et al. 2014) was identified by the committee. This record was manually added to the review. The search was amended to retrieve the paper and limited to the date of the original search. Line 4 of the original strategy was broadened to adjacency 3 and renal-cell* was amended to renal* to pick up the paper. Note that the results retrieved from the Embase top-up searches are less than the original search, the Embase search also retrieved additional papers published prior to 2024, unrelated to the change to line 4, this is due to the entry dates in several records being amended during the Embase reload.

Although top-up searches were carried out, no re-runs were carried out for review G.

Clinical searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	24/02/2025	Wiley	Issue 2 of 12, February 2025	76
Cochrane Database of Systematic Reviews (CDSR)	24/02/2025	Wiley	Issue 2 of 12, February 2025	1
Embase	24/02/2025	Ovid	1974 to 2025 February 20	2345
MEDLINE ALL	24/02/2025	Ovid	1946 to February 20, 2025	2102

Additional search methods

Who was contacted	A member of the committee
How contact was made	via email
When contact was made	15/05/2025
No. of results	1
Additional notes	The search was updated and rerun using the original date limits to expand the adjacency and to broaden the second set of terms for line 4 that covered succinate dehydrogenase renal carcinoma. The results from this search are documented in the top-up search results and the search history is available in the top-up search strategy history.

Top-up search results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	15/07/2025	Wiley	Issue 7 of 12, July 2025	77

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	15/07/2025	Wiley	Issue 7 of 12, July 2025	1
Embase	15/07/2025	Ovid	1974 to 2025 July 14	2351
MEDLINE ALL	15/07/2025	Ovid	1946 to July 14, 2025	2106

Search strategy history

Database name: Cochrane CENTRAL and CDSR

Searches	
#1	MeSH descriptor: [Kidney Neoplasms] explode all trees 1988
#2	MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees 717
#3	MeSH descriptor: [Genetic Predisposition to Disease] this term only 1785
#4	MeSH descriptor: [von Hippel-Lindau Disease] this term only 5
#5	#1 AND (#2 OR #3 OR #4) 125
#6	((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) NEAR/3 (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 1
#7	((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) NEAR/3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)):ti,ab 10
#8	(succinate-dehydrogenas* NEAR/2 (renal-cell* or RCC or ccRCC)):ti,ab 0
#9	{or #5-#8} 136
#10	(hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs):ti,ab 635
#11	((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) NEAR/1 (gene* or syndrom*)):ti,ab 1477
#12	#10 OR #11 2102
#13	(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 972
#14	(renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*):ti,ab 4379
#15	#12 and (#13 OR #14) 62
#16	#9 or #15 194
#17	MeSH descriptor: [Nephrectomy] explode all trees 583
#18	(nephrectom* or lymphadenectom*):ti,ab 3884
#19	MeSH descriptor: [Radiotherapy] this term only 1529
#20	MeSH descriptor: [Lymphatic Irradiation] this term only 91
#21	MeSH descriptor: [Radiosurgery] this term only 640

Searches	
#22	MeSH descriptor: [Radiotherapy, Adjuvant] this term only 1606
#23	MeSH descriptor: [Radiotherapy Dosage] this term only 2691
#24	MeSH descriptor: [Radiotherapy, High-Energy] this term only 333
#25	MeSH descriptor: [Re-Irradiation] this term only 40
#26	MeSH descriptor: [Cytoreduction Surgical Procedures] this term only 314
#27	MeSH descriptor: [Ablation Techniques] this term only 171
#28	MeSH descriptor: [Radiofrequency Ablation] this term only 206
#29	MeSH descriptor: [Robotic Surgical Procedures] this term only 1005
#30	MeSH descriptor: [Minimally Invasive Surgical Procedures] this term only 1438
#31	MeSH descriptor: [Metastasectomy] this term only 63
#32	MeSH descriptor: [Lymph Node Excision] this term only 1811
#33	MeSH descriptor: [Watchful Waiting] this term only 536
#34	((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) NEAR/3 (remov* or surg* or extract* or extirpat* or operat* or excis*)):ti,ab 20716
#35	((laproscop* or open or partial* or radical or transperiton* or retroperiton*) NEAR/3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)):ti,ab 68002
#36	(nephron* NEAR/2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)):ti,ab 128
#37	(radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR):ti,ab 67831
#38	((RAS or (robotic* NEAR/1 assist*)) NEAR/1 (surg* or remov* or partial* or procedur* or treat* or operat*)):ti,ab 289
#39	(minimal* NEAR/2 invas* NEAR/2 (surg* or procedur* or treat*)):ti,ab 3999
#40	((inferior-vena-cava or IVC) NEAR/2 thrombectom*):ti,ab 2
#41	((activ* or tumor* or tumour* or delay*) NEAR/2 monitor*):ti,ab 3348
#42	(delay* NEAR/2 treat*):ti,ab 3102
#43	(watchful* NEAR/1 wait*):ti,ab 708
#44	(surveil* or follow-up or followup):ti,ab 278599
#45	{or #17-#44} 405282
#46	#16 AND #45 in Trials 101
#47	"conference":pt or (clinicaltrials or trialsearch):so 804706
#48	#46 NOT #47 76
#49	#16 and #45 in Cochrane Reviews 1

Database name: Embase

Searches
1 exp kidney tumor/ and (genetic predisposition/ or von Hippel Lindau disease/ or birt hogg dube syndrome/ or inherited renal cancer-predisposing syndrome/ or tuberous sclerosis/) (9170)
2 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (464)

Searches
3 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)).ti,ab. (5010)
4 (succinate-dehydrogenas* adj2 (renal-cell* or RCC or ccRCC)).ti,ab. (83)
5 or/1-4 (13614)
6 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs).ti,ab. (32820)
7 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) adj1 (gene* or syndrom*)).ti,ab. (5791)
8 or/6-7 (36369)
9 (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. (25080)
10 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*).ti,ab. (153266)
11 or/9-10 (168320)
12 5 or (8 and 11) (17794)
13 exp nephrectomy/ (85594)
14 (nephrectom* or lymphadenectom*).ti,ab. (98605)
15 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) adj3 (remov* or surg* or extract* or extirpat* or operat* or excis*)).ti,ab. (345002)
16 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)).ti,ab. (1229180)
17 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)).ti,ab. (5033)
18 radiotherapy/ or cancer radiotherapy/ or adjuvant radiotherapy/ or exp radiosurgery/ or radiotherapy dosage/ or megavoltage radiotherapy/ or re-irradiation/ or cytoreductive surgery/ or ablation therapy/ or radiofrequency ablation/ or robot assisted surgery/ or minimally invasive surgery/ or metastasis resection/ or lymph node dissection/ or cryotherapy/ or stereotactic body radiation therapy/ or active surveillance/ or watchful waiting/ (770864)
19 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR).ti,ab. (1300825)
20 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (4461)
21 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (63840)
22 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (710)
23 ((activ* or tumo?r* or delay*) adj2 monitor*).ti,ab. (35477)
24 ((activ* or tumo?r* or delay*) and monitor*).kw. (258)
25 (delay* adj2 treat*).ti,ab. (35240)
26 (delay* and treat*).kw. (301)
27 (watchful* adj1 wait*).ti,ab. (5251)
28 (surveil* or follow-up or followup).ti,ab,kw. (2477667)
29 or/13-28 (5172662)
30 12 and 29 (6886)

Searches
31 nonhuman/ not human/ (5584609)
32 30 not 31 (6808)
33 limit 32 to english language (6172)
34 33 not (letter or editorial).pt. (6083)
35 34 not conference*.db,pt,su. (3933)
36 random:.tw. (2167351)
37 placebo:.mp. (549990)
38 double-blind:.tw. (257902)
39 or/36-38 (2453119)
40 (MEDLINE or pubmed).tw. (484078)
41 exp systematic review/ or systematic review.tw. (603747)
42 meta-analysis/ (344645)
43 intervention$.ti. (297976)
44 or/40-43 (1116208)
45 exp cohort analysis/ or exp epidemiology/ or exp clinical trial/ or exp evaluation study/ or statistics/ (7686454)
46 ((control and (study or group*)) or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp. (11541420)
47 or/45-46 (14941317)
48 39 or 44 or 47 (15946625)
49 35 and 48 (2372)
50 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1847439)

Searches
51 exp "organisation for economic co-operation and development"/ (3272)
52 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/ (3953619)
53 european union/ (33040)
54 developed country/ (36301)
55 or/51-54 (3989141)
56 50 not 55 (1683193)
57 49 not 56 (2345)

1 **Database name: Medline ALL**

Searches
1 exp Kidney Neoplasms/ and (exp Neoplastic Syndromes, Hereditary/ or Genetic Predisposition to Disease/ or von Hippel-Lindau Disease/) (12365)
2 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (274)
3 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)).ti,ab. (3526)
4 (succinate-dehydrogenas* adj2 (renal-cell* or RCC or ccRCC)).ti,ab. (60)
5 or/1-4 (15507)
6 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs).ti,ab. (23316)
7 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) adj1 (gene* or syndrom*)).ti,ab. (3711)
8 or/6-7 (25534)
9 (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. (17061)
10 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*).ti,ab. (108398)
11 or/9-10 (119167)
12 5 or (8 and 11) (19056)
13 exp nephrectomy/ (38909)
14 (nephrectom* or lymphadenectom*).ti,ab. (63108)
15 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) adj3 (remov* or surg* or extract* or extirpat* or operat* or excis*)).ti,ab. (240169)

Searches
16 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)).ti,ab. (966615)
17 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)).ti,ab. (2758)
18 radiotherapy/ or lymphatic irradiation/ or radiosurgery/ or radiotherapy, adjuvant/ or radiotherapy dosage/ or radiotherapy, high-energy/ or re-irradiation/ or Cytoreduction Surgical Procedures/ or Ablation Techniques/ or Radiofrequency Ablation/ or Robotic Surgical Procedures/ or Minimally Invasive Surgical Procedures/ or Metastasectomy/ or Lymph Node Excision/ or Watchful Waiting/ (250865)
19 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR).ti,ab. (970207)
20 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (2650)
21 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (42352)
22 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (312)
23 ((activ* or tumo?r* or delay*) adj2 monitor*).ti,ab. (24939)
24 ((activ* or tumo?r* or delay*) and monitor*).kw. (152)
25 (delay* adj2 treat*).ti,ab. (22673)
26 (delay* and treat*).kw. (186)
27 (watchful* adj1 wait*).ti,ab. (3419)
28 (surveil* or follow-up or followup).ti,ab,kw. (1588113)
29 or/13-28 (3628375)
30 12 and 29 (6236)
31 animals/ not humans/ (5273876)
32 30 not 31 (6154)
33 limit 32 to english language (5195)
34 limit 33 to (letter or historical article or comment or editorial or news or case reports) (1827)
35 33 not 34 (3368)
36 exp Randomized Controlled Trial/ (633776)
37 randomi?ed.mp. (1169120)
38 placebo.mp. (264489)
39 or/36-38 (1238346)
40 (MEDLINE or pubmed).tw. (394918)
41 systematic review.tw. (334876)
42 systematic review.pt. (284105)
43 meta-analysis.pt. (213171)
44 intervention$.ti. (229015)
45 or/40-44 (806748)
46 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (7020942)
47 ((control and (study or group*)) or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp. (9300119)
48 or/46-47 (12183669)
49 39 or 45 or 48 (12707663)
50 35 and 49 (2203)

Searches
51 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/ (1405060)
52 "organisation for economic co-operation and development"/ (661)
53 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/ (3640263)
54 european union/ (18369)
55 developed countries/ (21740)
56 or/52-55 (3656998)
57 51 not 56 (1312347)
58 50 not 57 (2102)
59 58 not overall.pt. (2102)

1 Top-up clinical search strategies

2 Database name: Cochrane CENTRAL and CDSR

Searches		
#1	MeSH descriptor: [Kidney Neoplasms] explode all trees	2031
#2	MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees	729
#3	MeSH descriptor: [Genetic Predisposition to Disease] this term only	1800

Searches
#4 MeSH descriptor: [von Hippel-Lindau Disease] this term only 6
#5 #1 AND (#2 OR #3 OR #4) 126
#6 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) NEAR/3 (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 1
#7 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) NEAR/3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)):ti,ab 11
#8 (succinate-dehydrogenas* NEAR/3 (renal* or RCC or ccRCC)):ti,ab 0
#9 {or #5-#8} 138
#10 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs):ti,ab 644
#11 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) NEAR/1 (gene* or syndrom*)):ti,ab 1522
#12 #10 OR #11 2156
#13 (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 996
#14 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*):ti,ab 4484
#15 #12 and (#13 OR #14) 65
#16 #9 or #15 199
#17 MeSH descriptor: [Nephrectomy] explode all trees 591
#18 (nephrectom* or lymphadenectom*):ti,ab 3992
#19 MeSH descriptor: [Radiotherapy] this term only 1520
#20 MeSH descriptor: [Lymphatic Irradiation] this term only 93
#21 MeSH descriptor: [Radiosurgery] this term only 667
#22 MeSH descriptor: [Radiotherapy, Adjuvant] this term only 1625
#23 MeSH descriptor: [Radiotherapy Dosage] this term only 2706
#24 MeSH descriptor: [Radiotherapy, High-Energy] this term only 332
#25 MeSH descriptor: [Re-Irradiation] this term only 42
#26 MeSH descriptor: [Cytoreduction Surgical Procedures] this term only 328
#27 MeSH descriptor: [Ablation Techniques] this term only 174
#28 MeSH descriptor: [Radiofrequency Ablation] this term only 230
#29 MeSH descriptor: [Robotic Surgical Procedures] this term only 1065
#30 MeSH descriptor: [Minimally Invasive Surgical Procedures] this term only 1460
#31 MeSH descriptor: [Metastasectomy] this term only 63
#32 MeSH descriptor: [Lymph Node Excision] this term only 1832
#33 MeSH descriptor: [Watchful Waiting] this term only 556
#34 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass

Searches
or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) NEAR/3 (remov* or surg* or extract* or extirpat* or operat* or excis*)):ti,ab 21508
#35 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) NEAR/3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)):ti,ab 69678
#36 (nephron* NEAR/2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)):ti,ab 131
#37 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR):ti,ab 69585
#38 ((RAS or (robotic* NEAR/1 assist*)) NEAR/1 (surg* or remov* or partial* or procedur* or treat* or operat*)):ti,ab 308
#39 (minimal* NEAR/2 invas* NEAR/2 (surg* or procedur* or treat*)):ti,ab 4211
#40 ((inferior-vena-cava or IVC) NEAR/2 thrombectom*):ti,ab 3
#41 ((activ* or tumor* or tumour* or delay*) NEAR/2 monitor*):ti,ab 3429
#42 (delay* NEAR/2 treat*):ti,ab 3178
#43 (watchful* NEAR/1 wait*):ti,ab 723
#44 (surveil* or follow-up or followup):ti,ab 287194
#45 {or #17-#44} 417181
#46 #16 AND #45 in Trials 104
#47 "conference":pt or (clinicaltrials or trialsearch):so 835703
#48 #46 NOT #47 with Cochrane Library publication date to Feb 2025, in Trials 77
#49 #16 and #45 with Cochrane Library publication date to Feb 2025, in Cochrane Reviews 1

1 **Database name: Embase**

Searches
1 exp kidney tumor/ and (genetic predisposition/ or von Hippel Lindau disease/ or birt hogg dube syndrome/ or inherited renal cancer-predisposing syndrome/ or tuberous sclerosis/) (9516)
2 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (479)
3 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)).ti,ab. (5138)
4 (succinate-dehydrogenas* adj3 (renal* or RCC or ccRCC)).ti,ab. (133)
5 or/1-4 (14113)
6 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs).ti,ab. (34111)
7 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) adj1 (gene* or syndrom*)).ti,ab. (6019)
8 or/6-7 (37808)
9 (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. (26649)

Searches
10 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*).ti,ab. (158936)
11 or/9-10 (174762)
12 5 or (8 and 11) (18424)
13 exp nephrectomy/ (88057)
14 (nephrectom* or lymphadenectom*).ti,ab. (101716)
15 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) adj3 (remov* or surg* or extract* or extirpat* or operat* or excis*)).ti,ab. (362895)
16 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)).ti,ab. (1279959)
17 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)).ti,ab. (5135)
18 radiotherapy/ or cancer radiotherapy/ or adjuvant radiotherapy/ or exp radiosurgery/ or radiotherapy dosage/ or megavoltage radiotherapy/ or re-irradiation/ or cytoreductive surgery/ or ablation therapy/ or radiofrequency ablation/ or robot assisted surgery/ or minimally invasive surgery/ or metastasis resection/ or lymph node dissection/ or cryotherapy/ or stereotactic body radiation therapy/ or active surveillance/ or watchful waiting/ (818687)
19 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR).ti,ab. (1361164)
20 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (4864)
21 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (68176)
22 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (736)
23 ((activ* or tumo?r* or delay*) adj2 monitor*).ti,ab. (38474)
24 ((activ* or tumo?r* or delay*) and monitor*).kw. (281)
25 (delay* adj2 treat*).ti,ab. (37652)
26 (delay* and treat*).kw. (318)
27 (watchful* adj1 wait*).ti,ab. (5552)
28 (surveil* or follow-up or followup).ti,ab,kw. (2630687)
29 or/13-28 (5443595)
30 12 and 29 (7164)
31 nonhuman/ not human/ (5732704)
32 30 not 31 (7083)
33 limit 32 to english language (6432)
34 33 not (letter or editorial).pt. (6341)
35 34 not conference*.db,pt,su. (4130)
36 random:.tw. (2458129)
37 placebo:.mp. (635037)
38 double-blind:.tw. (323199)
39 or/36-38 (2764076)

Searches
40 (MEDLINE or pubmed).tw. (507427)
41 exp systematic review/ or systematic review.tw. (633123)
42 meta-analysis/ (365393)
43 intervention$.ti. (329199)
44 or/40-43 (1187484)
45 exp cohort analysis/ or exp epidemiology/ or exp clinical trial/ or exp evaluation study/ or statistics/ (8468423)
46 ((control and (study or group*)) or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp. (12118291)
47 or/45-46 (15898338)
48 39 or 44 or 47 (16932389)
49 35 and 48 (2538)
50 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1918037)
51 exp "organisation for economic co-operation and development"/ (3488)
52 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/ (4052767)
53 european union/ (33775)

Searches
54 developed country/ (37188)
55 or/51-54 (4089242)
56 50 not 55 (1748034)
57 49 not 56 (2508)
58 (197* or 198* or 199* or 200* or 201* or 2020* or 2021* or 2022* or 2023* or 2024* or 202501* or 2025020* or 2025021* or "20250221" or "20250222" or "20250223" or "20250224").dc,dd. (42646892)
59 57 and 58 (2351)

Database name: Medline ALL

Searches
1 exp Kidney Neoplasms/ and (exp Neoplastic Syndromes, Hereditary/ or Genetic Predisposition to Disease/ or von Hippel-Lindau Disease/) (12469)
2 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (279)
3 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)).ti,ab. (3598)
4 (succinate-dehydrogenas* adj3 (renal* or RCC or ccRCC)).ti,ab. (101)
5 or/1-4 (15709)
6 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs).ti,ab. (23926)
7 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) adj1 (gene* or syndrom*)).ti,ab. (3813)
8 or/6-7 (26196)
9 (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. (17549)
10 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*).ti,ab. (110488)
11 or/9-10 (121557)
12 5 or (8 and 11) (19353)
13 exp nephrectomy/ (39295)
14 (nephrectom* or lymphadenectom*).ti,ab. (64215)
15 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) adj3 (remov* or surg* or extract* or extirpat* or operat* or excis*)).ti,ab. (245228)
16 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)).ti,ab. (984769)
17 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)).ti,ab. (2813)

Searches
18 radiotherapy/ or lymphatic irradiation/ or radiosurgery/ or radiotherapy, adjuvant/ or radiotherapy dosage/ or radiotherapy, high-energy/ or re-irradiation/ or Cytoreduction Surgical Procedures/ or Ablation Techniques/ or Radiofrequency Ablation/ or Robotic Surgical Procedures/ or Minimally Invasive Surgical Procedures/ or Metastasectomy/ or Lymph Node Excision/ or Watchful Waiting/ (255463)
19 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR).ti,ab. (990290)
20 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (2893)
21 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (44028)
22 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (327)
23 ((activ* or tumo?r* or delay*) adj2 monitor*).ti,ab. (25624)
24 ((activ* or tumo?r* or delay*) and monitor*).kw. (161)
25 (delay* adj2 treat*).ti,ab. (23528)
26 (delay* and treat*).kw. (198)
27 (watchful* adj1 wait*).ti,ab. (3487)
28 (surveil* or follow-up or followup).ti,ab,kw. (1632952)
29 or/13-28 (3713093)
30 12 and 29 (6350)
31 animals/ not humans/ (5323181)
32 30 not 31 (6266)
33 limit 32 to english language (5304)
34 limit 33 to (letter or historical article or comment or editorial or news or case reports) (1860)
35 33 not 34 (3444)
36 exp Randomized Controlled Trial/ (643905)
37 randomi?ed.mp. (1198079)
38 placebo.mp. (268966)
39 or/36-38 (1268176)
40 (MEDLINE or pubmed).tw. (416953)
41 systematic review.tw. (355371)
42 systematic review.pt. (299468)
43 meta-analysis.pt. (215741)
44 intervention$.ti. (237727)
45 or/40-44 (843842)
46 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (7150980)
47 ((control and (study or group*)) or (time and factors) or cohort or program or comparative stud* or evaluation studies or survey* or follow-up* or ci).mp. (9501507)
48 or/46-47 (12428726)
49 39 or 45 or 48 (12975556)
50 35 and 49 (2249)

Searches
51 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/ (1440749)
52 "organisation for economic co-operation and development"/ (686)
53 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/ (3686542)
54 european union/ (18541)
55 developed countries/ (21846)
56 or/52-55 (3703477)
57 51 not 56 (1347091)
58 50 not 57 (2146)
59 58 not overall.pt. (2146)
60 59 and (1946* or 1947* or 1948* or 1949* or 195* or 196* or 197* or 198* or 199* or 200* or 201* or 2020* or 2021* or 2022* or 2023* or 2024* or 202501* or 2025020* or 2025021* or "20250221" or "20250222" or "20250223" or "20250224").ed,dt. (2106)

1 1.

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
EconLit	03/03/2025	Ovid	1886 to February 20, 2025	0
Embase	03/03/2025	Ovid	1974 to 2025 February 28	143
International Health Technology Assessment Database from INAHTA	03/03/2025	https://database.inahta.org/	n/a	6
MEDLINE ALL	03/03/2025	Ovid	1946 to February 28, 2025	43

Search strategy history

Database name: Econlit

Searches
1 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (0)
2 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)).ti,ab. (0)
3 (succinate-dehydrogenas* adj2 (renal-cell* or RCC or ccRCC)).ti,ab. (0)
4 or/1-3 (0)
5 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs).ti,ab. (30)
6 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) adj1 (gene* or syndrom*)).ti,ab. (14)
7 or/5-6 (44)
8 (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)
9 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*).ti,ab. (27)
10 or/8-9 (35)

Searches
11 4 or (7 and 10) (0)
12 (nephrectom* or lymphadenectom*).ti,ab. (0)
13 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) adj3 (remov* or surg* or extract* or extirpat* or operat* or excis*)).ti,ab. (87)
14 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)).ti,ab. (27473)
15 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)).ti,ab. (0)
16 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR).ti,ab. (648)
17 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (12)
18 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (9)
19 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (0)
20 ((activ* or tumo?r* or delay*) adj2 monitor*).ti,ab. (376)
21 ((activ* or tumo?r* or delay*) and monitor*).kw. (3)
22 (delay* adj2 treat*).ti,ab. (54)
23 (delay* and treat*).kw. (0)
24 (watchful* adj1 wait*).ti,ab. (10)
25 (surveil* or follow-up or followup).ti,ab,kw. (4284)
26 or/12-25 (32813)
27 11 and 26 (0)

Database name: Embase

Searches
1 exp Kidney Neoplasms/ and (exp Neoplastic Syndromes, Hereditary/ or Genetic Predisposition to Disease/ or von Hippel-Lindau Disease/) (9187)
2 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (463)
3 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)).ti,ab. (5021)
4 (succinate-dehydrogenas* adj2 (renal-cell* or RCC or ccRCC)).ti,ab. (82)
5 or/1-4 (13455)
6 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs).ti,ab. (32905)
7 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) adj1 (gene* or syndrom*)).ti,ab. (5793)
8 or/6-7 (36458)
9 (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. (25153)

Searches
10 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*).ti,ab. (153747)
11 or/9-10 (168860)
12 5 or (8 and 11) (18381)
13 exp nephrectomy/ (85853)
14 (nephrectom* or lymphadenectom*).ti,ab. (99032)
15 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) adj3 (remov* or surg* or extract* or extirpat* or operat* or excis*)).ti,ab. (346437)
16 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)).ti,ab. (1235340)
17 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)).ti,ab. (5037)
18 radiotherapy/ or lymphatic irradiation/ or radiosurgery/ or radiotherapy, adjuvant/ or radiotherapy dosage/ or radiotherapy, high-energy/ or re-irradiation/ or Cytoreduction Surgical Procedures/ or Ablation Techniques/ or Radiofrequency Ablation/ or Robotic Surgical Procedures/ or Minimally Invasive Surgical Procedures/ or Metastasectomy/ or Lymph Node Excision/ or Watchful Waiting/ (509256)
19 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR).ti,ab. (1306117)
20 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (4468)
21 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (63946)
22 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (710)
23 ((activ* or tumo?r* or delay*) adj2 monitor*).ti,ab. (35595)
24 ((activ* or tumo?r* or delay*) and monitor*).kw. (258)
25 (delay* adj2 treat*).ti,ab. (35360)
26 (delay* and treat*).kw. (297)
27 (watchful* adj1 wait*).ti,ab. (5258)
28 (surveil* or follow-up or followup).ti,ab,kw. (2482656)
29 or/13-28 (5102394)
30 12 and 29 (6897)
31 animals/ not humans/ (1238823)
32 30 not 31 (6892)
33 limit 32 to english language (6272)
34 limit 33 to (letter or historical article or comment or editorial or news or case reports) [Limit not valid in Embase; records were retained] (78)
35 33 not 34 (6194)
36 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

Searches
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/ (1839625)
37 "organisation for economic co-operation and development"/ (3263)
38 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/ (3918897)
39 european union/ (33077)
40 developed countries/ (36508)
41 or/37-40 (3954719)
42 36 not 41 (1678463)
43 35 not 42 (6121)
44 43 not overall*.pt. (6121)
45 Cost-Benefit Analysis/ (98789)
46 Quality-Adjusted Life Years/ (39653)
47 Markov Chains/ (12822)
48 exp Models, Economic/ (4772)
49 cost*.ti. (207987)
50 (cost* adj2 utilit*).tw. (13970)
51 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (425396)
52 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (73431)
53 (qualit* adj2 adjust* adj2 life*).tw. (30150)
54 QALY*.tw. (29637)
55 (incremental* adj2 cost*).tw. (31503)
56 ICER.tw. (14688)
57 utilities.tw. (16409)
58 markov*.tw. (43810)

Searches
59 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (78677)
60 ((utility or effective*) adj2 analys*).tw. (41648)
61 (willing* adj2 pay*).tw. (16620)
62 (EQ5D* or EQ-5D*).tw. (29559)
63 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (6086)
64 (european* adj2 quality adj3 ("5" or five)).tw. (1140)
65 or/45-64 (740248)
66 (quality adjusted or adjusted life year$).ti,ab,kf. (39739)
67 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (30355)
68 (illness state$1 or health state$1).ti,ab,kf. (16167)
69 (hui or hui1 or hui2 or hui3).ti,ab,kf. (3512)
70 (multiattribute$ or multi attribute$).ti,ab,kf. (1745)
71 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (35840)
72 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (48907)
73 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (3880)
74 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (37028)
75 quality of life/ and ec.fs. (71655)
76 quality of life/ and (health adj3 status).ti,ab,kf. (23280)
77 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ (7264)
78 or/66-77 (250951)
79 Economics/ (245473)
80 Value of life/ (174021)
81 exp "Costs and Cost Analysis"/ (431780)
82 exp Economics, Hospital/ (1115453)
83 exp Economics, Medical/ (1115453)
84 Economics, Nursing/ (37101)
85 Economics, Pharmaceutical/ (16467)
86 exp "Fees and Charges"/ (46140)
87 exp Budgets/ (35833)
88 budget*.ti,ab. (51446)
89 (economic* or pharmaco?economic*).ti. (82760)
90 (price* or pricing*).ti,ab. (80248)
91 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. (322210)
92 (financ* or fee or fees).ti,ab. (260038)
93 (value adj2 (money or monetary)).ti,ab. (4460)
94 or/79-93 (1826374)
95 65 or 78 or 94 (2203465)
96 44 and 95 (143)

Database name: INAHTA

Searches		
Lines	Search query	Hits
#1	"kidney neoplasms"[mhe]	130
#2	"neoplastic syndromes hereditary"[mhe]	44
#3	"genetic predisposition to disease"[mh]	60
#4	"von hippel-lindau disease"[mh]	3
#5	#4 or #3 or #2	95
#6	#5 and #1	0
#7	((heredit* or inherit* or genetic* or bilateral* or multifocal* or "multi-focal"*) AND (kidney* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*)))	4
#8	((heredit* or inherit* or genetic* or bilateral* or multifocal* or "multi-focal*") AND ("renal-cell*" or rcc or ccrcc or "renal-carcinoma*" or "renal-cancer*" or "renal-mass*" or "renal-tumo?r*" or "grawitz-tumo?r*" or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*))	3
#9	("succinate-dehydrogenas*" AND ("renal-cell*" or rcc or ccrcc))	0
#10	#9 OR #8 OR #7 OR #6	6
#11	("hippel-lindau" or vhl or "birt-hogg"-dube or bhds or "tuberous-sclerosis" or tsc or flcn or bap1 or "bap-1" or hprc or hlrcc or bsrm or brsms)	24
#12	((pgl or pcc or met or flcn or tsc1 or tsc2 or fh or sdha) AND (gene* or syndrom*))	174
#13	#12 OR #11	197
#14	(kidney* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))	52
#15	("renal-cell*" or rcc or ccrcc or "renal-carcinoma*" or "renal-cancer*" or "renal-mass*" or "renal-tumo?r*" or "grawitz-tumo?r*" or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)	126
#16	#15 OR #14	166
#17	#16 AND #13	3
#18	#17 OR #10	7
#19	"nephrectomy"[mhe]	14
#20	(nephrectom* or lymphadenectom*)	37
#21	"radiotherapy"[mh]	248
#22	"lymphatic irradiation"[mh]	0
#23	"radiosurgery"[mh]	72
#24	"radiotherapy adjuvant"[mh]	28
#25	"radiotherapy dosage"[mh]	44
#26	"radiotherapy high-energy"[mh]	9
#27	"re-irradiation"[mh]	2
#28	"cytoreduction surgical procedures"[mh]	6
#29	"ablation techniques"[mh]	66
#30	"robotic surgical procedures"[mh]	34
#31	"minimally invasive surgical procedures"[mh]	156
#32	"metastasectomy"[mh]	1
#33	"lymph node excision"[mh]	11

Searches
#34 "watchful waiting"[mh] 16
#35 "radiofrequency ablation"[mh] 67
#36 ((kidney* or renal* or rcc or ccrcc or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) AND (remov* or surg* or extract* or extirpat* or operat* or excis*))946
#37 (laproscop* or open or partial* or radical or transperiton* or retroperiton*) AND (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)) 875
#38 (nephron* AND (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)) 2
#39 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or sabr)1068
#40 ((ras or (robotic* AND assist*)) AND (surg* or remov* or partial* or procedur* or treat* or operat*)) 80
#41 (minimal* AND invas* AND (surg* or procedur* or treat*))262
#42 (("inferior-vena"-cava or ivc) AND thrombectom*) 0
#43 ((activ* or tumor* or tumour* or delay*) AND monitor*) 281
#44 (delay* AND treat*) 239
#45 (watchful* AND wait*) 43
#46 (surveil* or "follow-up" or followup) 1621
#47 #46 OR #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 4177
#48 #47 and #18 6

1 **Database name: Medline ALL**

Searches
1 exp Kidney Neoplasms/ and (exp Neoplastic Syndromes, Hereditary/ or Genetic Predisposition to Disease/ or von Hippel-Lindau Disease/) (12368)
2 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (274)
3 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)).ti,ab. (3536)
4 (succinate-dehydrogenas* adj2 (renal-cell* or RCC or ccRCC)).ti,ab. (60)
5 or/1-4 (15520)
6 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs).ti,ab. (23360)
7 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) adj1 (gene* or syndrom*)).ti,ab. (3718)
8 or/6-7 (25580)
9 (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. (17084)

Searches
10 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*).ti,ab. (108533)
11 or/9-10 (119317)
12 5 or (8 and 11) (19074)
13 exp nephrectomy/ (38920)
14 (nephrectom* or lymphadenectom*).ti,ab. (63170)
15 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) adj3 (remov* or surg* or extract* or extirpat* or operat* or excis*)).ti,ab. (240491)
16 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)).ti,ab. (967723)
17 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)).ti,ab. (2762)
18 radiotherapy/ or lymphatic irradiation/ or radiosurgery/ or radiotherapy, adjuvant/ or radiotherapy dosage/ or radiotherapy, high-energy/ or re-irradiation/ or Cytoreduction Surgical Procedures/ or Ablation Techniques/ or Radiofrequency Ablation/ or Robotic Surgical Procedures/ or Minimally Invasive Surgical Procedures/ or Metastasectomy/ or Lymph Node Excision/ or Watchful Waiting/ (251105)
19 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR).ti,ab. (971524)
20 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (2662)
21 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (42453)
22 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (314)
23 ((activ* or tumo?r* or delay*) adj2 monitor*).ti,ab. (24970)
24 ((activ* or tumo?r* or delay*) and monitor*).kw. (152)
25 (delay* adj2 treat*).ti,ab. (22723)
26 (delay* and treat*).kw. (187)
27 (watchful* adj1 wait*).ti,ab. (3423)
28 (surveil* or follow-up or followup).ti,ab,kw. (1590804)
29 or/13-28 (3633572)
30 12 and 29 (6240)
31 animals/ not humans/ (5276957)
32 30 not 31 (6158)
33 limit 32 to english language (5199)
34 limit 33 to (letter or historical article or comment or editorial or news or case reports) (1829)
35 33 not 34 (3370)
36 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

Searches
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/ (1407071)
37 "organisation for economic co-operation and development"/ (662)
38 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/ (3643226)
39 european union/ (18388)
40 developed countries/ (21747)
41 or/37-40 (3659974)
42 36 not 41 (1314285)
43 35 not 42 (3261)
44 43 not overall*.pt. (3261)
45 Cost-Benefit Analysis/ (97063)
46 Quality-Adjusted Life Years/ (17503)
47 Markov Chains/ (16866)
48 exp Models, Economic/ (16754)
49 cost*.ti. (155869)
50 (cost* adj2 utilit*).tw. (8572)
51 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (312803)
52 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (53014)
53 (qualit* adj2 adjust* adj2 life*).tw. (19899)
54 QALY*.tw. (16168)
55 (incremental* adj2 cost*).tw. (19375)
56 ICER.tw. (7006)
57 utilities.tw. (10359)
58 markov*.tw. (35021)

Searches
59 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (58616)
60 ((utility or effective*) adj2 analys*).tw. (27993)
61 (willing* adj2 pay*).tw. (11332)
62 (EQ5D* or EQ-5D*).tw. (15707)
63 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4637)
64 (european* adj2 quality adj3 ("5" or five)).tw. (846)
65 or/45-64 (555634)
66 (quality adjusted or adjusted life year$).ti,ab,kf. (27730)
67 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (16617)
68 (illness state$1 or health state$1).ti,ab,kf. (9285)
69 (hui or hui1 or hui2 or hui3).ti,ab,kf. (2191)
70 (multiattribute$ or multi attribute$).ti,ab,kf. (1561)
71 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (22943)
72 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (28851)
73 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (2637)
74 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (17509)
75 quality of life/ and ec.fs. (11248)
76 quality of life/ and (health adj3 status).ti,ab,kf. (12958)
77 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ (18605)
78 or/66-77 (118223)
79 Economics/ (27545)
80 Value of life/ (5834)
81 exp "Costs and Cost Analysis"/ (276772)
82 exp Economics, Hospital/ (26126)
83 exp Economics, Medical/ (14458)
84 Economics, Nursing/ (4013)
85 Economics, Pharmaceutical/ (3156)
86 exp "Fees and Charges"/ (31626)
87 exp Budgets/ (14323)
88 budget*.ti,ab. (39184)
89 (economic* or pharmaco?economic*).ti. (66895)
90 (price* or pricing*).ti,ab. (59391)
91 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. (238725)
92 (financ* or fee or fees).ti,ab. (181541)
93 (value adj2 (money or monetary)).ti,ab. (3361)
94 or/79-93 (756509)
95 65 or 78 or 94 (1021981)
96 44 and 95 (43)

Top up cost effectiveness searches

Database name: Econlit

Searches
1 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (0)
2 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)).ti,ab. (0)
3 (succinate-dehydrogenas* adj3 (renal* or RCC or ccRCC)).ti,ab. (0)
4 or/1-3 (0)
5 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs).ti,ab. (30)
6 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) adj1 (gene* or syndrom*)).ti,ab. (14)
7 or/5-6 (44)
8 (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)
9 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*).ti,ab. (28)
10 or/8-9 (36)
11 4 or (7 and 10) (0)
12 (nephrectom* or lymphadenectom*).ti,ab. (0)
13 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) adj3 (remov* or surg* or extract* or extirpat* or operat* or excis*)).ti,ab. (90)
14 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)).ti,ab. (27884)
15 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)).ti,ab. (0)
16 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR).ti,ab. (661)
17 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (13)
18 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (9)
19 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (0)
20 ((activ* or tumo?r* or delay*) adj2 monitor*).ti,ab. (384)
21 ((activ* or tumo?r* or delay*) and monitor*).kw. (3)
22 (delay* adj2 treat*).ti,ab. (55)
23 (delay* and treat*).kw. (0)
24 (watchful* adj1 wait*).ti,ab. (10)
25 (surveil* or follow-up or followup).ti,ab,kw. (4365)

Searches
26 or/12-25 (33328)
27 11 and 26 (0)
28 (18* or 19* or 200* or 201* or 2020* or 2021* or 2022* or 2023* or 2024* or 202501* or 202502* or "20250301" or "20250302" or "20250303").up. (2053387)
29 27 and 28 (0)

2.

Database name: Embase

Searches
1 exp kidney tumor/ and (genetic predisposition/ or von Hippel Lindau disease/ or birt hogg dube syndrome/ or inherited renal cancer-predisposing syndrome/ or tuberous sclerosis/) (9516)
2 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (479)
3 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)).ti,ab. (5138)
4 (succinate-dehydrogenas* adj3 (renal* or RCC or ccRCC)).ti,ab. (133)
5 or/1-4 (14113)
6 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs).ti,ab. (34111)
7 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) adj1 (gene* or syndrom*)).ti,ab. (6019)
8 or/6-7 (37808)
9 (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. (26649)
10 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*).ti,ab. (158936)
11 or/9-10 (174762)
12 5 or (8 and 11) (18424)
13 exp nephrectomy/ (88057)
14 (nephrectom* or lymphadenectom*).ti,ab. (101716)
15 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) adj3 (remov* or surg* or extract* or extirpat* or operat* or excis*)).ti,ab. (362895)
16 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)).ti,ab. (1279959)
17 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)).ti,ab. (5135)
18 radiotherapy/ or cancer radiotherapy/ or adjuvant radiotherapy/ or exp radiosurgery/ or radiotherapy dosage/ or megavoltage radiotherapy/ or re-irradiation/ or cytoreductive

Searches
surgery/ or ablation therapy/ or radiofrequency ablation/ or robot assisted surgery/ or minimally invasive surgery/ or metastasis resection/ or lymph node dissection/ or cryotherapy/ or stereotactic body radiation therapy/ or active surveillance/ or watchful waiting/ (818687)
19 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR).ti,ab. (1361164)
20 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (4864)
21 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (68176)
22 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (736)
23 ((activ* or tumo?r* or delay*) adj2 monitor*).ti,ab. (38474)
24 ((activ* or tumo?r* or delay*) and monitor*).kw. (281)
25 (delay* adj2 treat*).ti,ab. (37652)
26 (delay* and treat*).kw. (318)
27 (watchful* adj1 wait*).ti,ab. (5552)
28 (surveil* or follow-up or followup).ti,ab,kw. (2630687)
29 or/13-28 (5443595)
30 12 and 29 (7164)
31 nonhuman/ not human/ (5732704)
32 30 not 31 (7083)
33 limit 32 to english language (6432)
34 33 not (letter or editorial).pt. (6341)
35 34 not conference*.db,pt,su. (4130)
36 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or

Searches
vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1918037)
37 exp "organisation for economic co-operation and development"/ (3488)
38 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/ (4052767)
39 european union/ (33775)
40 developed country/ (37188)
41 or/37-40 (4089242)
42 36 not 41 (1748034)
43 35 not 42 (4093)
44 cost utility analysis/ (14270)
45 quality adjusted life year/ (41116)
46 cost*.ti. (213600)
47 (cost* adj2 utilit*).tw. (14715)
48 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (453395)
49 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (77711)
50 (qualit* adj2 adjust* adj2 life*).tw. (31317)
51 QALY*.tw. (30673)
52 (incremental* adj2 cost*).tw. (32738)
53 ICER.tw. (15221)
54 utilities.tw. (16876)
55 markov*.tw. (45035)
56 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (82316)
57 ((utility or effective*) adj2 analys*).tw. (44112)
58 (willing* adj2 pay*).tw. (17261)
59 (EQ5D* or EQ-5D*).tw. (32578)
60 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (6661)
61 (european* adj2 quality adj3 ("5" or five)).tw. (1271)
62 or/44-61 (735085)
63 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (31413)
64 (illness state$1 or health state$1).ti,ab,kf. (16646)
65 (hui or hui1 or hui2 or hui3).ti,ab,kf. (3747)
66 (multiattribute$ or multi attribute$).ti,ab,kf. (1815)

Searches
67 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (37632)
68 utilities.ti,ab,kf. (17118)
69 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or euroqol or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. (39367)
70 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. (11166)
71 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (52565)
72 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (4023)
73 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (39835)
74 quality of life/ and ec.fs. (74041)
75 quality of life/ and (health adj3 status).ti,ab,kf. (25847)
76 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ (7675)
77 or/63-76 (281886)
78 Health economics/ (37487)
79 exp health care cost/ (374550)
80 exp Fee/ (46912)
81 exp Budget/ (36922)
82 Funding/ (83041)
83 budget*.ti,ab. (53313)
84 (economic* or pharmaco?economic*).ti. (85359)
85 (price* or pricing*).ti,ab. (82936)
86 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. (344379)
87 (financ* or fee or fees).ti,ab. (274616)
88 (value adj2 (money or monetary)).ti,ab. (4619)
89 or/78-88 (1136506)
90 62 or 77 or 89 (1600464)
91 43 and 90 (73)
92 91 and (197* or 198* or 199* or 200* or 201* or 2020* or 2021* or 2022* or 2023* or 2024* or 202501* or 202502* or "20250301" or "20250302" or "20250303").dc,dd. (68)

3.

Database name: INAHTA

Searches

4.

1 **Database name: Medline ALL**

Searches
1 exp Kidney Neoplasms/ and (exp Neoplastic Syndromes, Hereditary/ or Genetic Predisposition to Disease/ or von Hippel-Lindau Disease/) (12469)
2 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*))).ti,ab. (279)
3 ((heredit* or inherit* or genetic* or bilateral* or multifocal* or multi-focal*) adj3 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*)).ti,ab. (3598)
4 (succinate-dehydrogenas* adj3 (renal* or RCC or ccRCC)).ti,ab. (101)
5 or/1-4 (15709)
6 (hippel-lindau or VHL or birt-hogg-dube or BHDS or Tuberous-sclerosis or TSC or FLCN or BAP1 or BAP-1 or HPRC or HLRCC or BSRM or BRSMs).ti,ab. (23926)
7 ((PGL or PCC or MET or FLCN or TSC1 or TSC2 or FH or SDHA) adj1 (gene* or syndrom*)).ti,ab. (3813)
8 or/6-7 (26196)
9 (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. (17549)
10 (renal-cell* or RCC or ccRCC or renal-carcinoma* or renal-cancer* or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma* or leiomyomatosis* or paraganglioma* or pheochromocytoma*).ti,ab. (110488)
11 or/9-10 (121557)
12 5 or (8 and 11) (19353)
13 exp nephrectomy/ (39295)
14 (nephrectom* or lymphadenectom*).ti,ab. (64215)
15 ((kidney* or renal* or RCC or ccRCC or lymph* or adrenal* or cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) adj3 (remov* or surg* or extract* or extirpat* or operat* or excis*)).ti,ab. (245228)
16 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat* or excis*)).ti,ab. (984769)
17 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv* or excis*)).ti,ab. (2813)
18 radiotherapy/ or lymphatic irradiation/ or radiosurgery/ or radiotherapy, adjuvant/ or radiotherapy dosage/ or radiotherapy, high-energy/ or re-irradiation/ or Cytoreduction Surgical Procedures/ or Ablation Techniques/ or Radiofrequency Ablation/ or Robotic Surgical Procedures/ or Minimally Invasive Surgical Procedures/ or Metastasectomy/ or Lymph Node Excision/ or Watchful Waiting/ (255463)
19 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or SABR).ti,ab. (990290)
20 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (2893)
21 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (44028)
22 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (327)

Searches
23 ((activ* or tumo?r* or delay*) adj2 monitor*).ti,ab. (25624)
24 ((activ* or tumo?r* or delay*) and monitor*).kw. (161)
25 (delay* adj2 treat*).ti,ab. (23528)
26 (delay* and treat*).kw. (198)
27 (watchful* adj1 wait*).ti,ab. (3487)
28 (surveil* or follow-up or followup).ti,ab,kw. (1632952)
29 or/13-28 (3713093)
30 12 and 29 (6350)
31 animals/ not humans/ (5323181)
32 30 not 31 (6266)
33 limit 32 to english language (5304)
34 limit 33 to (letter or historical article or comment or editorial or news or case reports) (1860)
35 33 not 34 (3444)
36 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/ (1440749)
37 "organisation for economic co-operation and development"/ (686)
38 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/ (3686542)

Searches
39 european union/ (18541)
40 developed countries/ (21846)
41 or/37-40 (3703477)
42 36 not 41 (1347091)
43 35 not 42 (3333)
44 43 not overall*.pt. (3333)
45 Cost-Benefit Analysis/ (98340)
46 Quality-Adjusted Life Years/ (18101)
47 Markov Chains/ (17248)
48 exp Models, Economic/ (16907)
49 cost*.ti. (158828)
50 (cost* adj2 utilit*).tw. (8823)
51 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (325297)
52 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (54834)
53 (qualit* adj2 adjust* adj2 life*).tw. (20538)
54 QALY*.tw. (16727)
55 (incremental* adj2 cost*).tw. (19995)
56 ICER.tw. (7335)
57 utilities.tw. (10579)
58 markov*.tw. (36012)
59 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (59890)
60 ((utility or effective*) adj2 analys*).tw. (29023)
61 (willing* adj2 pay*).tw. (11788)
62 (EQ5D* or EQ-5D*).tw. (16405)
63 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4893)
64 (european* adj2 quality adj3 ("5" or five)).tw. (887)
65 or/45-64 (573263)
66 (quality adjusted or adjusted life year$).ti,ab,kf. (29359)
67 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (17189)
68 (illness state$1 or health state$1).ti,ab,kf. (9469)
69 (hui or hui1 or hui2 or hui3).ti,ab,kf. (2248)
70 (multiattribute$ or multi attribute$).ti,ab,kf. (1616)
71 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (23730)
72 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (29460)
73 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (2726)
74 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (18034)
75 quality of life/ and ec.fs. (11473)

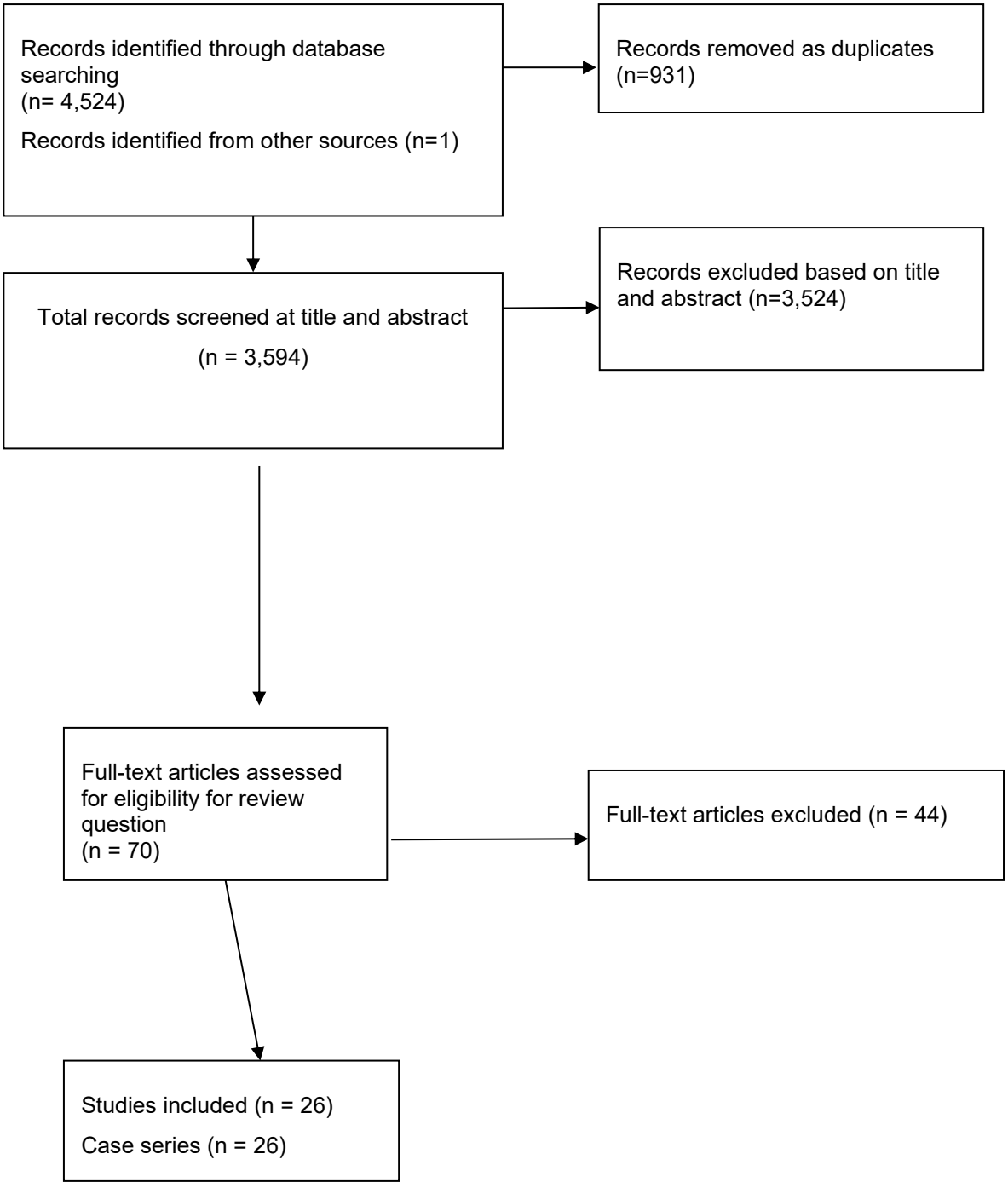
Searches
76 quality of life/ and (health adj3 status).ti,ab,kf. (13249)
77 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ (19145)
78 or/66-77 (122192)
79 Economics/ (27548)
80 Value of life/ (5838)
81 exp "Costs and Cost Analysis"/ (280426)
82 exp Economics, Hospital/ (26247)
83 exp Economics, Medical/ (14464)
84 Economics, Nursing/ (4013)
85 Economics, Pharmaceutical/ (3168)
86 exp "Fees and Charges"/ (31717)
87 exp Budgets/ (14375)
88 budget*.ti,ab. (40079)
89 (economic* or pharmaco?economic*).ti. (68408)
90 (price* or pricing*).ti,ab. (60861)
91 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. (248908)
92 (financ* or fee or fees).ti,ab. (187664)
93 (value adj2 (money or monetary)).ti,ab. (3451)
94 or/79-93 (776811)
95 65 or 78 or 94 (1050262)
96 44 and 95 (44)
97 96 and (1946* or 1947* or 1948* or 1949* or 195* or 196* or 197* or 198* or 199* or 200* or 201* or 2020* or 2021* or 2022* or 2023* or 2024* or 202501* or 202502* or "20250301" or "20250302" or "20250303").ed,dt. (43)

1

2

Appendix C – Effectiveness evidence study selection

Figure 1: PRISMA diagram



Appendix D – Effectiveness evidence

Allasia, 2017

Bibliographic Reference	Allasia, Marco; Soria, Francesco; Battaglia, Antonino; Gazzera, Carlo; Calandri, Marco; Caprino, Mirko Parasiliti; Lucatello, Barbara; Velrti, Andrea; Maccario, Mario; Pasini, Barbara; Bosio, Andrea; Gontero, Paolo; Destefanis, Paolo; Radiofrequency Ablation for Renal Cancer in Von Hippel-Lindau Syndrome Patients: A Prospective Cohort Analysis.; Clinical genitourinary cancer; 2017

Study details

Study type	Case series
Study location	Italy
Study setting	Multidisciplinary VHL care unit
Study dates	January 2000 to June 2016
Sources of funding	Not reported
Inclusion criteria	People suspected of having VHL or with family history of VHL People with renal cell carcinoma
Intervention(s)	Radiofrequency ablation 19 procedures were carried out under ultrasound and 1 with laparoscopic radiofrequency ablation
Comparator	None
Outcome measures	Overall survival Cancer-specific survival New-onset CKD
Number of participants	n = 9 (20 treatments)
Follow-up frequency	Follow-up after treatment usually consisted of MRI and/or CT scan of the abdomen, and X-ray or CT scan of the chest every 3 months for the first year, every 6 months for the second year, and annually thereafter.
Duration of follow-up	Median 102 months (IQR 68-165)
Loss to follow-up	None reported
Methods of analysis	Mann-Whitney U test was performed to analyse pre- and posttreatment changes in creatinine.
Additional comments	Methods state that lesions larger than 1 cm are usually eligible for active treatment, and that the first choice is usually percutaneous ablation with US-guided RFA. The

	methods also stated that the feasibility of RFA is established considering RCC volume and location, and the cut-off diameter for RFA eligibility is 4 cm. People received genetic testing upon access to the VHL unit, and the report did not state that any participants tested negative.

Characteristics

Study-level characteristics

Characteristic	Study (N = 9)
Lesion type - Solid Total lesions = 20 Sample size	n = 18 ; % = 90
Lesion type - Cystic Total lesions = 20 Sample size	n = 2 ; % = 10
Size of lesion (cm) Total lesions = 20 Median (IQR)	2.5 (2 to 3)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design, reporting of study population, and reporting of funding.)*
Overall Risk of Bias	Applicability	Directly applicable

Bodard, 2022

Bibliographic Reference	Bodard, Sylvain; Boudhabhay, Idris; Dariane, Charles; Delavaud, Christophe; Guinebert, Sylvain; Joly, Dominique; Timsit, Marc-Olivier; Mejean, Arnaud; Verkarre, Virginie; Helenon, Olivier; Richard, Stephane; Correas, Jean-Michel; Percutaneous Thermal Ablation for Renal Tumors in Patients with Birt-Hogg-Dube Syndrome.; Cancers; 2022; vol. 14 (no. 20)

Study details

Study type	Case series
Study location	France

Study setting	Not reported
Study dates	January 2007 to May 2021
Sources of funding	No external funding
Inclusion criteria	People with BHD syndrome People with proven germline FLCN mutation People who underwent thermal ablation for a renal tumour
Intervention(s)	Percutaneous thermal ablation (17 radiofrequency ablations, 1 microwave ablation and 1 cryoablation) performed using ultrasound and CT guidance
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Distant recurrence New-onset CKD Need for dialysis or renal transplant
Number of participants	n= 6 (19 renal tumours; 14 ablation sessions)
Follow-up frequency	Unenhanced and triphasic CE-CT and CE-MRI performed the following morning and at 2, 6, and 12 months after the procedure and then annually.
Duration of follow-up	Median 74 months (range: 33- 83)
Loss to follow-up	None reported
Methods of analysis	Categorical variables were reported as counts and percentages and continuous variables as means (SD) or median (range).
Additional comments	Nineteen renal tumours were treated including 7 chromophobe RCCs, 5 clear-cell RCCs, 4 papillary RCCs, 2 clear-cell papillary RCC, and one hybrid oncocytic/chromophobe tumour.

1

2 **haracteristics**

3 **Study-level characteristics**

Characteristic	**Study (N = 6)**
% Female Sample size	n = 1 ; % = 17
Mean age (SD) Mean (SD)	66 (11)
History of nephrectomy - Partial nephrectomy Sample size	n = 4 ; % = 67

Characteristic	Study (N = 6)
History of nephrectomy - Radical nephrectomy Sample size	n = 1 ; % = 17
Tumours per participant Number of renal tumours = 19 Median (IQR)	2 (1 to 3)
Tumour size (mm) Number of renal tumours = 19 Mean (SD)	21 (11)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	Moderate *(Serious concerns around study design and reporting of eligibility criteria.)*
Overall Risk of Bias	Applicability	Directly applicable

Bratslavsky, 2008

Bibliographic Reference	Bratslavsky, Gennady; Liu, Jack J; Johnson, Aaron D; Sudarshan, Sunil; Choyke, Peter L; Linehan, W Marston; Pinto, Peter A; Salvage partial nephrectomy for hereditary renal cancer: feasibility and outcomes.; The Journal of urology; 2008; vol. 179 (no. 1); 67-70

Study details

Study type	Case series
Study location	The US
Study setting	National Cancer Institute
Study dates	1999 to 2006
Sources of funding	Intramural Research Program of the National Institutes of Health
Inclusion criteria	People who underwent at least 3 partial nephrectomies on the same renal unit
Intervention(s)	Salvage partial nephrectomy
Comparator	None

Outcome measures	Overall survival Cancer-specific survival Distant recurrence Need for dialysis or renal transplant
Number of participants	n = 11 (13 salvage nephrectomies)
Follow-up frequency	Not reported
Duration of follow-up	Median 25 months (range 3 to 83)
Loss to follow-up	None reported
Methods of analysis	Outcomes were reported as number of participants
Additional comments	The title and abstract refer to hereditary renal cancer and VHL, however, the article does not report that any of the participants were tested for gene mutations. 7 of the 11 participants had a contralateral kidney, however, 6 of these participants had already undergone 2 previous partial nephrectomies on the contralateral side and 1 of the participants had undergone 3 prior ablations and had multiple remaining renal lesions.

Characteristics

Study-level characteristics

Characteristic	Study (N = 11)
% Female Sample size	n = 4 ; % = 36
Mean age (SD) Range	37 to 57
Mean age (SD) Median (IQR)	46 (NR to NR)
Number of tumours removed Range	1 to 27
Number of tumours removed Median (IQR)	5 (*NR* to *NR*)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious issues relating to study design and study population)*
Overall Risk of Bias	Applicability	Partially directly applicable *(The article does not describe whether participants were known to have a germline mutation)*

Chan, 2022

Bibliographic Reference	Chan, Vinson Wai-Shun; Lenton, James; Smith, Jonathan; Jagdev, Satinder; Ralph, Christy; Vasudev, Naveen; Bhattarai, Selina; Lewington, Andrew; Kimuli, Michael; Cartledge, Jon; Wah, Tze Min; Multimodal image-guided ablation on management of renal cancer in Von-Hippel-Lindau syndrome patients from 2004 to 2021 at a specialist centre: A longitudinal observational study.; European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology; 2022; vol. 48 (no. 3); 672-679

Study details

Study type	Case series
Study location	UK
Study setting	Specialist centre
Study dates	Dec 2004 to May 2021
Sources of funding	Not reported
Inclusion criteria	Aged over 18 years People with VHL People with T1a RCC (<4 cm)
Intervention(s)	Image-guided ablation: radiofrequency ablation (n=11), cryoablation (n=38), irreversible electroporation (n=9)
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Metastasis-free survival Distant recurrence New-onset CKD Need for dialysis or renal transplant
Number of participants	n=17 (54 RCCs)

Follow-up frequency	The standard MRI protocol included baseline, post-IGA at one month, 3-, 6- and 12-months. If the patient had a solitary kidney, earlier follow-up at one-week post-IGA was performed instead. After that, all patients were monitored six-monthly with MRI and annually with non-contrast enhanced CT thorax for up to 10 years.
Duration of follow-up	Median follow-up 79 months (IQR 51 to 134)
Loss to follow-up	None lost to follow-up
Methods of analysis	Kaplan Meier curves were used to present the 5- and 10-year OS, CS, LRFS and MFS.
Additional comments	7 participants had solitary kidneys at referral. During follow-up, 3 participants underwent radical nephrectomy, and 1 participant underwent partial nephrectomy. One participant with bilateral nephrectomies needed long-term dialysis.

Characteristics

Study-level characteristics

Characteristic	Study (N = 17)
% Female Sample size	n = 6 ; % = 35
Mean age (SD) Mean (SD)	43.9 (13.6)
eGFR at baseline (ml/min/1.73 m²) n=50 Mean (SD)	69.6 (22.9)
Previous surgery - Contralateral radical nephrectomy Sample size	n = 7 ; % = 41
Previous surgery - Partial nephrectomy Sample size	n = 3 ; % = 18
Tumour size (cm) n=54 Mean (SD)	2.1 (0.92)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	Moderate *(Serious concerns around study design and lack of reporting around funding)*

Section	Question	Answer
Overall Risk of Bias	Applicability	Partially directly applicable *(Interventions included irreversible electroporation 15%)*

Drachenberg, 2004

Bibliographic Reference	Drachenberg, Darrel E; Mena, Othon J; Choyke, Peter L; Linehan, W Marston; Walther, McClellan M; Parenchymal sparing surgery for central renal tumors in patients with hereditary renal cancers.; The Journal of urology; 2004; vol. 172 (no. 1); 49-53

Study details

Study type	Case series
Study location	The US
Study setting	Not reported
Study dates	1992 to 2000
Sources of funding	Not reported
Inclusion criteria	People with small hereditary central renal masses
Intervention(s)	Nephron sparing surgery
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Distant recurrence Need for dialysis or renal transplant
Number of participants	n = 32 (44 procedures)
Follow-up frequency	Not reported
Duration of follow-up	Median 33.7 months (range 1.5 to 101)
Loss to follow-up	Not reported
Methods of analysis	Outcomes reported as number of participants
Additional comments	Outcomes appeared to be reported for central tumours only

	Study included participants with VHL, HPRC carcinoma, FRO, BHD, and sporadic kidney cancer. No participant had metastatic disease at the time of surgery Out of 32 participants with central lesions, 10 underwent 2 separate surgeries on the index kidney and 1 underwent 3 surgeries on the index kidney.

Characteristics

Study-level characteristics

Characteristic	Study (N = 32)
% Female Sample size	n = 15 ; % = 46.9
Mean age (SD) Range	18 to 66
Mean age (SD) Mean (SD)	32.9 (*NR*)
Seum creatine at baseline (mg/dL) Range	0.6 to 1.8
Seum creatine at baseline (mg/dL) Mean (SD)	1.05 (*NR*)
Average tumour size (cm) Range	1.5 to 7.5
Average tumour size (cm) Mean (SD)	3.2 (*NR*)
Average number of tumours Range	1 to 16
Average number of tumours Sample size	n = 6.7
Heritable RCC - VHL Sample size	n = 26 ; % = 81
Heritable RCC - HPRC carcinoma Sample size	n = 3 ; % = 9

Characteristic	Study (N = 32)
Heritable RCC - FRO Sample size	n = 1 ; % = 3
Heritable RCC - BHD Sample size	n = 1 ; % = 3
Heritable RCC - Sporadic Sample size	n = 1 ; % = 3
Tumour stage - T1 No of events	n = 43 ; % = 93
Tumour stage - T2 No of events	n = 1 ; % = 2
Tumour stage - T3b No of events	n = 2 ; % = 4
Cell type - Clear No of events	n = 39 ; % = 85
Cell type - Other No of events	n = 7 ; % = 15
Tumour grade - Grade I No of events	n = 2 ; % = 4
Tumour grade - Grade II No of events	n = 40 ; % = 87
Tumour grade - Grade III No of events	n = 4 ; % = 9
Tumour grade - Grade IV No of events	n = 0 ; % = 0

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around the study design, and lack of reporting around the participant characteristics and sources of funding.)*

Section	Question	Answer
Overall Risk of Bias	Applicability	Partially directly applicable *(Outcomes were reported for a combination of heritable RCC conditions and could not be separated)*

Frydenberg, 1993

Bibliographic Reference	Frydenberg, M; Malek, R S; Zincke, H; Conservative renal surgery for renal cell carcinoma in von Hippel-Lindau's disease.; The Journal of urology; 1993; vol. 149 (no. 3); 461-4

Study details

Study type	Case series
Study location	The US
Study setting	Not reported
Study dates	1956 to 1991
Sources of funding	Not reported
Inclusion criteria	People with renal cell carcinoma People with VHL
Intervention(s)	Partial nephrectomy Radical nephrectomy Radical nephrectomy and contralateral partial nephrectomy
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Distant recurrence
Number of participants	n=19
Follow-up frequency	Follow-up of patients included regular (at least yearly) evaluation with physical examination, chest radiography and abdominal CT to detect any occult recurrences or metastasis.
Duration of follow-up	Mean 5 years (range 3 months to 14 years)
Loss to follow-up	Not reported
Methods of analysis	Not reported

Additional comments	At diagnosis no participants with renal cell carcinoma had evidence of metastatic disease. Of 5 participants with bilateral asynchronous renal cell carcinoma, 4 had contralateral local tumours identified 2 to 14 years after unilateral nephrectomy. All 4 participants had evidence of metastasis at diagnosis of the contralateral disease, and all died of the disease. Two of these participants did not receive the optimal yearly follow-up evaluation. Either locally recurrent tumours within the renal remnants or metastatic spread developed in 3 of 4 participants with large renal lesions (more than 5 cm), even if they were of low grade or stage.

Characteristics

Study-level characteristics

Characteristic	Study (N = 19)
% Female Sample size	n = 11 ; % = 58
Mean age (SD) Range	15 to 65
Mean age (SD) Mean (SD)	40.3 (*NR*)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design, reporting of study population, and reporting of funding and outcomes.)*
Overall Risk of Bias	Applicability	Directly applicable

Gaillard, 2020

Bibliographic Reference	Gaillard, Victor; Tricard, Thibault; Garnon, Julien; Cazzato, Roberto Luigi; Dalili, Danoob; Gangi, Afshin; Lang, Herve; Repeat ablative therapy in hereditary or multifocal renal cancer: Functional and oncological outcomes.; Urologic oncology; 2020; vol. 38 (no. 10); 797e15-797e20

Study details

Study type	Case series
Study location	France
Study setting	Not reported
Study dates	2007 to 2017
Sources of funding	Not reported
Inclusion criteria	People who underwent at least one percutaneous thermo-ablative intervention for a renal tumour People with a history of bilateral, multifocal or early occurring renal tumours (before 60 years)
Exclusion criteria	People undergoing thermal ablation for non-malignant tumours
Intervention(s)	Thermal ablation (32 treatments) - cryotherapy (24 treatments) or radiotherapy (8 treatments). Treatments were performed percutaneously under radiological control, except for one case performed by laparotomy.
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Distant recurrence New-onset CKD
Number of participants	n = 10 (57 lesions)
Follow-up frequency	MRI at one or three months, then nine months post-procedure and then annually.
Duration of follow-up	Mean 7.5 years (±4.9)
Loss to follow-up	Not reported
Methods of analysis	Categorical variables represented as number and frequency.
Additional comments	Ablative treatment was proposed if feasible i.e. when the tumour size was 1 cm or more.

	Treatment was unsuccessful in 2 cases and was subsequently managed by retreatment with thermal ablation. Following ablative treatment, 1 de novo tumour was treated with partial nephrectomy due to its large size (55 mm) and close proximity to bowel. There was an average of 3.2 ablative treatments per participants.

Characteristics

Study-level characteristics

Characteristic	Study (N = 10)
% Female Sample size	n = 6 ; % = 60
Mean age (SD) Mean (SD)	39.5 (8.9)
eGFR at baseline (ml/min/1.73 m²) Mean (SD)	95.8 (27.3)
Treated tumour size (mm) Mean (SD)	13.5 (9)
Heritable RCC - VHL Sample size	n = 6 ; % = 60
Heritable RCC - BHD Sample size	n = 1 ; % = 10
Heritable RCC - Chromosome 3 translocation Sample size	n = 1 ; % = 10
Heritable RCC - Bilateral recurrent tumours before 45 years Sample size	n = 2 ; % = 20

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design and lack of reporting around funding.)*
Overall Risk of Bias	Applicability	Partially directly applicable *(2 participants did not have a heritable condition, and results were not reported separately for different heritable conditions.)*

Gill, 2014

Bibliographic Reference	Gill AJ; Hes O; Papathomas T; Šedivcová M; Tan PH; Agaimy A; Andresen PA; Kedziora A; Clarkson A; Toon CW; Sioson L; Watson N; Chou A; Paik J; Clifton-Bligh RJ; Robinson BG; Benn DE; Hills K; Maclean F; Niemeijer ND; Vlatkovic L; Hartmann A; Corssmit EP; van Leenders GJ; Przybycin C; McKenney JK; Magi-Galluzzi C; Yilmaz A; Yu D; Nicoll KD; Yong JL; Sibony M; Yakirevich E; Fleming S; Chow CW; Miettinen M; Michal M; Trpkov K; Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients.; The American journal of surgical pathology; 2014; vol. 38 (no. 12)

Study details

Study type	Case series
Study location	North America, Europe, Asia, and Australia
Study setting	Not reported
Study dates	NR
Sources of funding	Cancer Institute New South Wales and Czech Republic Government grant agency
Inclusion criteria	People with RCC and proven SDH mutation or suspected SDH deficiency on the basis of morphology, immunohistochemistry, or a personal or family history of paragangliomas or SDH-deficient GIST
Intervention(s)	• Radical nephrectomy • Partial nephrectomy • Total nephrectomy and contralateral wedge resection
Comparator	NA
Outcome measures	Overall survival Cancer-specific survival Distant recurrence
Number of participants	12 people with 17 RCCs [previously unpublished cases with recorded intervention]
Follow-up frequency	NR
Duration of follow-up	Mean 55 months (range 0 to 368 months)
Loss to follow-up	NA
Methods of analysis	NA
Additional comments	At presentation all tumours with known size and stage were confined to the kidney.

	Two people with metastasis had unbiopsied neoplasms in the contralateral kidney, which were identified at the time of presentation with metastasis.

Characteristics

Study-level characteristics

Characteristic	Study (N = 14)
% Female Baseline data relates to all participants including 2 participants that were not included in this review as they had no recorded intervention. Sample size	n = 6 ; % = 42.9
Mean age (SD) Baseline data relates to all participants including 2 participants that were not included in this review as they had no recorded intervention. Range	14 to 76
Mean age (SD) Baseline data relates to all participants including 2 participants that were not included in this review as they had no recorded intervention. Mean (SD)	39.8 (NR)
Tumour size (mm) Baseline data relates to all participants including 2 participants that were not included in this review as they had no recorded intervention. Range	7 to 90
Tumour size (mm) Baseline data relates to all participants including 2 participants that were not included in this review as they had no recorded intervention. Mean (SD)	51 (NR)

Quality appraisal and risk of bias

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Study was conducted retrospectively. There was little detail on the interventions, and it was judged unlikely that assessors were blinded to the interventions. Follow-up was under 6 months for half of the participants, and there was no evidence for adverse events.)*
Overall Risk of Bias	Applicability	Directly applicable

1

2 ## Grubb, 2007

Bibliographic Reference	Grubb, Robert L 3rd; Franks, Michael E; Toro, Jorge; Middelton, Lindsay; Choyke, Lynda; Fowler, Sarah; Torres-Cabala, Carlos; Glenn, Gladys M; Choyke, Peter; Merino, Maria J; Zbar, Berton; Pinto, Peter A; Srinivasan, Ramaprasad; Coleman, Jonathan A; Linehan, W Marston; Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer.; The Journal of urology; 2007; vol. 177 (no. 6); 2074-80

3

4 ## Study details

Study type	Case series
Study location	The US
Study setting	National Cancer Institute
Study dates	1996 to September 2005
Sources of funding	Not reported
Inclusion criteria	Participants with renal tumours who had the longest follow-up Families at risk for HLRCC A family was defined as being affected with HLRCC if it contained 1 or more members affected with cutaneous leiomyomas or a germline mutation of the FH gene.
Intervention(s)	Radical nephrectomy Partial nephrectomy Radical and partial nephrectomy for bilateral lesions
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Distant recurrence
Number of participants	n=15 (the study reported on 19 participants, however, outcome data was only extracted for participants with non-metastatic disease at baseline)
Follow-up frequency	Not reported
Duration of follow-up	Median follow-up of 34 months (range 6 to 141)
Loss to follow-up	Not reported
Methods of analysis	NA

Additional comments	Participants with localized, solid renal tumours were recommended to undergo surgical resection. Only lesions 1 cm or greater and enhancing more than 20 HU that were predominantly solid were considered renal tumours.

Characteristics

Arm-level characteristics

Characteristic	Radical nephrectomy (N = 12)	Partial nephrectomy (N = 2)	Radical and partial nephrectomy (N = 1)
% Female Metastatic participants only Sample size	n = 8 ; % = 67	n = 0 ; % = 0	n = 0 ; % = 0
Mean age (SD) Characteristics for metastatic and non-metastatic participants (n=19) Range	23 to 67	46 to 64	38 to 38
Mean age (SD) Characteristics for metastatic and non-metastatic participants (n=19) Median (IQR)	41 (*NR* to *NR*)	55 (*NR* to *NR*)	38 (*NR* to *NR*)
Renal tumour size (cm) Range	2.3 to 10	1.5 to 1.5	8 to 15
Renal tumour size (cm) Median (IQR)	7 (*NR* to *NR*)	1.5 (*NR* to *NR*)	*NR* (*NR* to *NR*)
Tumour grade - T1a Sample size	n = 2 ; % = 17	n = 2 ; % = 100	n = 0 ; % = 0
Tumour grade - T1b Sample size	n = 2 ; % = 17	n = 0 ; % = 0	n = 0 ; % = 0
Tumour grade - T2 Sample size	n = 1 ; % = 8	n = 0 ; % = 0	n = 1 ; % = 100
Tumour grade - T3a Sample size	n = 5 ; % = 42	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	Radical nephrectomy (N = 12)	Partial nephrectomy (N = 2)	Radical and partial nephrectomy (N = 1)
Tumour grade - T3b Sample size	n = 2 ; % = 17	n = 0 ; % = 0	n = 0 ; % = 0
Tumour stage - Stage I Sample size	n = 1 ; % = 8	n = 2 ; % = 100	n = 0 ; % = 0
Tumour stage - Stage II Sample size	n = 1 ; % = 8	n = 0 ; % = 0	n = 1 ; % = 100
Tumour stage - Stage III Sample size	n = 8 ; % = 67	n = 0 ; % = 0	n = 0 ; % = 0
Tumour stage - Stage IV Sample size	n = 2 ; % = 17	n = 0 ; % = 0	n = 0 ; % = 0

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design, and lack of reporting around study participants, intervention, adverse events, and funding.)*
Overall Risk of Bias	Applicability	Directly applicable

Gupta, 2010

Bibliographic Reference	Gupta, Gopal N; Peterson, James; Thakore, Kailash N; Pinto, Peter A; Linehan, W Marston; Bratslavsky, Gennady; Oncological outcomes of partial nephrectomy for multifocal renal cell carcinoma greater than 4 cm.; The Journal of urology; 2010; vol. 184 (no. 1); 59-63

Study details

Study type	Case series
Study location	The US
Study setting	Not reported
Study dates	1995 to 2008

Sources of funding	Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research
Inclusion criteria	People with multifocal renal masses with the largest solid renal tumours greater than 4 cm People with germline mutations of VHL, BHD, or Met genes leading to clinical diagnosis of VHL, BHD or HPRC
Intervention(s)	Partial nephrectomy
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Metastasis-free survival Distant recurrence
Number of participants	n = 58 (60 surgeries)
Follow-up frequency	Participants were followed up at 3 months and at least once yearly after the first visit
Duration of follow-up	Median 45 months (range 2 to 163)
Loss to follow-up	No attrition
Methods of analysis	Probabilities of overall and cancer specific survival were depicted using the Kaplan-Meier method.
Additional comments	At the time of surgery, no participants had preoperative or intraoperative suspicion of locally advanced or metastatic disease Eight participants underwent prior partial nephrectomy on the ipsilateral kidney while 20 participants underwent prior partial nephrectomy on the contralateral kidney. Twenty participants underwent subsequent partial nephrectomy on the contralateral kidney and only one underwent subsequent radio frequency ablation.

Characteristics

Study-level characteristics

Characteristic	**Study (N = 58)**
% Female Sample size	n = 36 ; % = 62
Mean age (SD) Range	18.5 to 63.3
Mean age (SD)	43.7 (*NR*)

Characteristic	Study (N = 58)
Mean (SD)	
Number of tumours resected Range	1 to 44
Number of tumours resected Mean (SD)	6.4 (*NR*)
Largest tumour size (cm) Range	4 to 13
Largest tumour size (cm) Mean (SD)	5.3 (*NR*)
TNM staging - T1b Sample size	n = 52 ; % = 87
TNM staging - T2 Sample size	n = 8 ; % = 13
Heritable RCC - VHL Sample size	n = 41 ; % = 71
Heritable RCC - BHD Sample size	n = 10 ; % = 17
Heritable RCC - HPRC Sample size	n = 7 ; % = 11
Histological subtype - Clear cell Sample size	n = 44 ; % = 73.3
Histological subtype - Papillary type I Sample size	n = 7 ; % = 11.7
Histological subtype - Chromophobe Sample size	n = 5 ; % = 8.3
Histological subtype - Hybrid Sample size	n = 3 ; % = 5
Histological subtype - Oncocytic Sample size	n = 1 ; % = 1.7

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design, reporting of results and reporting of competing interests.)*
Overall Risk of Bias	Applicability	Partially directly applicable *(Results not reported separately for heritable RCC conditions.)*

Hes, 1999

Bibliographic Reference	Hes, F J; Slootweg, P J; van Vroonhoven, T J; Hene, R J; Feldberg, M A; Zewald, R A; Ploos van Amstel, J K; Hoppener, J W; Pearson, P L; Lips, C J; Management of renal cell carcinoma in von Hippel-Lindau disease.; European journal of clinical investigation; 1999; vol. 29 (no. 1); 68-75

Study details

Study type	Case series
Study location	The Netherlands
Study setting	University Hospital Utrecht
Study dates	1976 to 1997
Sources of funding	Dutch Prevention Fund
Inclusion criteria	People had VHL family history and fulfilled VHL criteria People with renal cell carcinoma
Intervention(s)	Partial nephrectomy Radical nephrectomy
Comparator	None
Outcome measures	New-onset CKD Need for dialysis or renal transplant
Number of participants	Radical nephrectomy n=3 Partial nephrectomy n=5 Two participants did not have surgery, however, one of these participants had metastatic disease at the start of the study
Follow-up frequency	Yearly follow-up included physical examination, abdominal radiology (ultrasonography and MRI) and biochemical analysis of blood (including serum creatinine assessment) and urine.

Duration of follow-up	Radical nephrectomy: mean follow-up 171 months (97 to 259) Partial nephrectomy: mean follow-up 30 months (range 21 to 52)
Loss to follow-up	Not reported
Methods of analysis	NA
Additional comments	Data extracted for non-metastatic participants 7 participants were from one family One patient remained on dialysis and the other had transplantation as both participants had both kidneys removed by radical nephrectomy

Characteristics

Study-level characteristics

Characteristic	Study (N = 10)
Mean age (SD) Range	24 to 45
Mean age (SD) Mean (SD)	32 (*NR*)
Number of tumours per kidney Range	0 to 14
Number of tumours per kidney Mean (SD)	4.6 (*NR*)

Arm-level characteristics

Characteristic	Partial nephrectomy (N = 5)	Radical nephrectomy (N = 3)
Largest lesion (cm) Range	1 to 5.5	1.4 to 14
Largest lesion (cm) Median (IQR)	2.6 (*NR* to *NR*)	2.3 (*NR* to *NR*)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design and lack of reporting around study population, intervention, outcomes and sources of support.)*
Overall Risk of Bias	Applicability	Directly applicable

Iwamoto, 2011

Bibliographic Reference	Iwamoto, Yoichi; Kanda, Hideki; Yamakado, Koichiro; Soga, Norihito; Arima, Kiminobu; Takeda, Kan; Sugimura, Yoshiki; Management of renal tumors in Von Hippel-Lindau disease by percutaneous CT fluoroscopic guided radiofrequency ablation: preliminary results.; Familial cancer; 2011; vol. 10 (no. 3); 529-34

Study details

Study type	Case series
Study location	Japan
Study setting	Not reported
Study dates	December 2002 to September 2009
Sources of funding	Not reported
Inclusion criteria	People with renal cell carcinoma Confirmed by previous nephrectomy, needle biopsy, and radiological findings. People with VHL • People with a family history of VHL and a CNS hemangioblastoma, phaeochromocytoma or clear cell RCC • People without a family history of VHL with two or more CNS hemangioblastomas or one CNS hemangioblastoma and a visceral tumour
Intervention(s)	Percutaneous CT fluoroscopic guided radiofrequency ablation
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Distant recurrence
Number of participants	n=7 (12 RCCs)
Follow-up frequency	Routine physical examination, laboratory tests as well as follow-up imaging at 1 week and 3-, 6- and 12-months following treatment and every 6 months thereafter.

Duration of follow-up	Mean follow-up 22 ± 11 months (range 12 to 46 months)
Loss to follow-up	Not reported
Methods of analysis	NA
Additional comments	1 participant had a single kidney due to a previous radical nephrectomy.

Characteristics

Study-level characteristics

Characteristic	Study (N = 7)
% Female Sample size	n = 5 ; % = 71
Mean age (SD) (years) Range	29 to 53
Mean age (SD) (years) Mean (SD)	43 (8.6)
eGFR at baseline (ml/min) Mean (SD)	65.3 (10.9)
Maximum tumour diameter (cm) Range	1 to 3.6
Maximum tumour diameter (cm) Mean (SD)	1.9 (0.8)
Number of tumours - Single tumour Sample size	n = 4 ; % = 57
Number of tumours - Multiple tumours Sample size	n = 3 ; % = 43

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	Moderate *(Serious concerns around study design and lack of reporting around competing interests and sources of support.)*
Overall Risk of Bias	Applicability	Directly applicable

Johnson, 2008

Bibliographic Reference	Johnson, Aaron; Sudarshan, Sunil; Liu, Jack; Linehan, W Marston; Pinto, Peter A; Bratslavsky, Gennady; Feasibility and outcomes of repeat partial nephrectomy.; The Journal of urology; 2008; vol. 180 (no. 1); 89-93

Study details

Study type	Case series
Study location	The US
Study setting	Not reported
Study dates	1992 to 2006
Sources of funding	Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research
Inclusion criteria	People with recurrent kidney tumours
Intervention(s)	Repeat partial nephrectomy 3 procedures were performed laparoscopically
Comparator	None
Outcome measures	Overall survival Distant recurrence Need for dialysis or renal transplant
Number of participants	n=47 (51 partial nephrectomies on the same unit)
Follow-up frequency	Not reported
Duration of follow-up	Median follow-up 56 months
Loss to follow-up	Not reported
Methods of analysis	NA
Additional comments	Forty-eight (94%) treatments were performed on patients with VHL. 1 participant had metastatic disease at the time of repeat partial nephrectomy. Most cases had previous history of contralateral kidney or non-renal abdominal surgery One third of the surgeries were performed on participant with a solitary kidney.

Characteristics

Study-level characteristics

Characteristic	Study (N = 47)
% Female Sample size	n = 14 ; % = 30
Mean age (SD) Range	20 to 70
Mean age (SD) Median (IQR)	44 (*NR* to *NR*)
Creatinine clearance (ml/min) Range	44.6 to 149.7
Creatinine clearance (ml/min) Median (IQR)	95.3 (*NR* to *NR*)
Number of tumours removed Range	1 to 55
Number of tumours removed Median (IQR)	7 (*NR* to *NR*)
Size of largest solid tumour (cm) Range	0.9 to 8
Size of largest solid tumour (cm) Median (IQR)	3.5 (*NR* to *NR*)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design and lack of reporting around intervention, outcomes, eligibility criteria and competing interests.)*

Section	Question	Answer
Overall Risk of Bias	Applicability	Partially directly applicable *(Only 94% of participants had VHL and 1 participant had metastatic disease at time of repeated partial nephrectomy)*

Kirste, 2022

Bibliographic Reference	Kirste, Simon; Ruhle, Alexander; Zschiedrich, Stefan; Schultze-Seemann, Wolfgang; Jilg, Cordula A; Neumann-Haefelin, Elke; Lo, Simon S; Grosu, Anca-Ligia; Kim, Emily; Stereotactic Body Radiotherapy for Renal Cell Carcinoma in Patients with Von Hippel-Lindau Disease-Results of a Prospective Trial.; Cancers; 2022; vol. 14 (no. 20)

Study details

Study type	Case series
Study location	Germany
Study setting	Tertiary cancer centre
Study dates	February 2016 to June 2018
Sources of funding	No funding
Inclusion criteria	People with a genetic diagnosis of VHL People with a progressive renal tumour with ≥1.5 cm in diameter and typical features of RCC on MRI and/or CT
Exclusion criteria	CKD stage IV or worse Previous radiotherapy
Intervention(s)	Stereotactic body radiotherapy
Comparator	None
Outcome measures	Overall survival Cancer-specific survival New-onset CKD Need for dialysis or renal transplant
Number of participants	n=7 (8 lesions)
Follow-up frequency	During therapy, participants were monitored weekly. During follow-up, participants were examined every 3 to 6 months. At follow-up, participants had a medical history, physical examination, and imaging of the abdomen, and toxicity was monitored.
Duration of follow-up	Median follow-up 43 months (range 18 to 54 months)

Loss to follow-up	Not reported
Methods of analysis	OS and CCS were determined following Kaplan-Meier analyses. Participants were censored at the follow-up visit.
Additional comments	This was a prospective study.

Characteristics

Study-level characteristics

Characteristic	Study (N = 7)
% Female Sample size	n = 4 ; % = 57.1
Mean age (SD) Range	36 to 56
Mean age (SD) Median (IQR)	44 (*NR* to *NR*)
eGFR at baseline (ml/min/1.73 m²) Mean (SD)	83.7 (13)
Prior kidney surgery - Partial nephrectomy Sample size	n = 3 ; % = 42.9
Prior kidney surgery - Adrenalectomy Sample size	n = 1 ; % = 14.3
Prior kidney surgery - None Sample size	n = 3 ; % = 42.9
Tumour size, largest (cm) Range	1.9 to 3.5
Tumour size, largest (cm) Median (IQR)	2.8 (*NR* to *NR*)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	Low
Overall Risk of Bias	Applicability	Directly applicable

Lund, 1994

Bibliographic Reference	Lund, G O; Fallon, B; Curtis, M A; Williams, R D; Conservative surgical therapy of localized renal cell carcinoma in von Hippel-Lindau disease.; Cancer; 1994; vol. 74 (no. 9); 2541-5

Study details

Study type	Case series
Study location	The US
Study setting	Not reported
Study dates	February 1983 to February 1993
Sources of funding	Not reported
Inclusion criteria	People with VHL People with asymptomatic renal masses
Intervention(s)	Partial nephrectomy (including enucleation) Partial nephrectomy (including enucleation) and radical nephrectomy: in one participant radical nephrectomy was performed alongside partial nephrectomy at initial treatment
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Distant recurrence Need for dialysis or renal transplant
Number of participants	• Partial nephrectomy n=9 • Radical nephrectomy and partial nephrectomy n=1 [Total of 72 tumours]
Follow-up frequency	Unclear, however, the discussion section states that it is important that yearly CT is conducted.
Duration of follow-up	Mean follow-up 62 months (range 11 to 118 months)
Loss to follow-up	Not reported
Methods of analysis	Not reported
Additional comments	Participants were identified from 14 families with VHL. All participants were free of metastatic disease preoperatively. Two participants had a single recurrence, and two participants had two recurrences each, which were treated by further surgery (one of these participants underwent radical nephrectomy).

	One participant who died from metastatic RCC did not attend follow-up appointments.

Characteristics

Study-level characteristics

Characteristic	Study (N = 10)
% Female Sample size	n = 4 ; % = 40
Mean age (SD) Range	23 to 49
Mean age (SD) Mean (SD)	33 (*NR*)
Serum Creatinine (mg/dL) Range	0.9 to 1.1
Serum Creatinine (mg/dL) Mean (SD)	1 (*NR*)
Tumour size - Smaller than 2 cm No of events	n = 61 ; % = 84.7
Tumour size - 2 to 4 cm No of events	n = 7 ; % = 9.7
Tumour size - Larger than 4 cm No of events	n = 4 ; % = 5.5

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design and lack of reporting around participant characteristics, intervention, outcomes, and competing interests and sources of support.)*
Overall Risk of Bias	Applicability	Directly applicable

Matsui, 2019

Bibliographic Reference	Matsui, Y; Hiraki, T; Gobara, H; Iguchi, T; Tomita, K; Uka, M; Araki, M; Nasu, Y; Furuya, M; Kanazawa, S; Percutaneous thermal ablation for renal cell carcinoma in patients with Birt-Hogg-Dube syndrome.; Diagnostic and interventional imaging; 2019; vol. 100 (no. 11); 671-677

Study details

Study type	Case series
Study location	Japan
Study setting	Inpatient
Study dates	June 2003 to July 2017
Sources of funding	No funding
Inclusion criteria	People with BHD syndrome With proven FLCN gene mutation People who underwent percutaneous thermal ablation for RCC
Intervention(s)	Thermal ablation performed percutaneously under CT fluoroscopy guidance Radiofrequency ablation (7 sessions for 14 RCCs) was conducted until 2011 and cryoablation (13 sessions for 15 RCCs) was used from April 2012
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Distant recurrence New-onset CKD Need for dialysis or renal transplant
Number of participants	n=6 (29 RCCs)
Follow-up frequency	CT was performed at 1-, 3-, and 6-months after the procedure and at 6- to 12-month intervals thereafter
Duration of follow-up	Median follow-up 54 months (range 6 to 173 months)
Loss to follow-up	None reported
Methods of analysis	NA
Additional comments	Once a new RCC developed, it was observed, and ablation was typically considered when it became larger than 1 to 2 cm

Characteristics

Study-level characteristics

Characteristic	Study (N = 6)
% Female Sample size	n = 2 ; % = 33
Mean age (SD) Mean (SD)	57.3 (7.5)
History of surgery - Radical nephrectomy Sample size	n = 2 ; % = 33
History of surgery - Partial nephrectomy Sample size	n = 1 ; % = 17
History of surgery - No nephrectomy Sample size	n = 3 ; % = 50
Number of RCCs per participant Range	1 to 16
Number of RCCs per participant Mean (SD)	4.8 (*NR*)
RCC size (mm) Mean (SD)	13.9 (4.6)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	Moderate *(Serious concerns around study design)*
Overall Risk of Bias	Applicability	Directly applicable

Matsukawa, 2024

Bibliographic Reference	Matsukawa, A.; Yanagisawa, T.; Shimizu, K.; Shariat, S.F.; Kimura, T.; Miki, J.; Percutaneous cryoablation of renal cell carcinomas in patients with Von Hippel-Lindau disease: Functional and oncological outcomes; International Journal of Urology; 2024; vol. 31 (no. 4); 448

Study details

Study type	Case series

Study location	Japan
Study setting	Not reported
Study dates	February 2014 to June 2022
Sources of funding	Not reported
Inclusion criteria	People with VHL People who underwent percutaneous cryoablation for small RCCs
Intervention(s)	Percutaneous cryoablation
Comparator	None
Outcome measures	Distant recurrence
Number of participants	n=14 (40 tumours)
Follow-up frequency	Not reported
Duration of follow-up	Median follow-up 57.5 months (IQR 25.0 to 76.5)
Loss to follow-up	Not reported
Methods of analysis	NA
Additional comments	None

Characteristics

Study-level characteristics

Characteristic	**Study (N = 14)**
% Female Sample size	n = 6 ; % = 43
Mean age (SD) Median (IQR)	45 (38 to 53)
eGFR at baseline (ml/min/1.73 m²) Median (IQR)	69 (59.8 to 88.7)
Previous surgery - Radical nephrectomy Sample size	n = 2 ; % = 14
Previous surgery - Partial nephrectomy Sample size	n = 5 ; % = 36

Characteristic	Study (N = 14)
Tumour diameter (mm) Median (IQR)	23 (17.75 to 27.25)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design and lack of clarity around eligibility criteria)*
Overall Risk of Bias	Applicability	Directly applicable

Novick, 1992

Bibliographic Reference	Novick, A C; Streem, S B; Long-term followup after nephron sparing surgery for renal cell carcinoma in von Hippel-Lindau disease.; The Journal of urology; 1992; vol. 147 (no. 6); 1488-90

Study details

Study type	Case series
Study location	The US
Study setting	Not reported
Study dates	1981 to 1986
Sources of funding	Not reported
Inclusion criteria	People with VHL People with localised bilateral renal cell carcinoma People who underwent nephron sparing surgery
Intervention(s)	Nephron sparing surgery
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Distant recurrence Need for dialysis or renal transplant
Number of participants	n=9

Follow-up frequency	Periodic follow-up with physical examination, renal function tests, chest x-ray and abdominal CT or ultrasound.
Duration of follow-up	Mean follow-up 7.2 years (range 43 to 120 months)
Loss to follow-up	Not reported
Methods of analysis	NA
Additional comments	Treatment of 8 participants was either preceded or followed by radical nephrectomy and 1 participant underwent bilateral partial nephrectomy.

Characteristics

Study-level characteristics

Characteristic	Study (N = 9)
Mean age (SD) Range	26 to 67
Serum Creatinine (mg/dL) Range	0.9 to 1.6
Pathological tumour stage - Stage I Sample size	n = 8 ; % = 89
Pathological tumour stage - Stage III Sample size	n = 1 ; % = 11

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design and lack of reporting around participant characteristics, adverse events, and competing interests and sources of support.)*
Overall Risk of Bias	Applicability	Directly applicable

Osman, 2023

Bibliographic Reference	Osman, F.H.; Chan, V.W.-S.; Breen, D.J.; King, A.; Nielsen, T.K.; Garnon, J.; Alcorn, D.; Lagerveld, B.; Graumann, O.; Keeley, F.X.; Walkden, M.; de Kerviler, E.; Wah, T.M.; Oncological and Peri-Operative Outcomes of Percutaneous Cryoablation of Renal Cell Carcinoma for Patients with Hereditary RCC Diseases-

An Analysis of European Multi-Centre Prospective EuRECA Registry; Cancers; 2023; vol. 15 (no. 13); 3322

Study details

Study type	Case series
Study location	Denmark, France, Netherlands, UK [EuRECA Registry]
Study setting	Not reported
Study dates	2015 to 2021
Sources of funding	Boston Scientific
Inclusion criteria	People with inherited RCC syndromes People with localised cT1aN0M0 or cT1bN0M0 cT1a and cT1b renal masses were defined as having maximum tumour diameters of ≤4 cm and >4 cm and ≤7 cm, respectively, on radiological imaging People treated with percutaneous cryoablation
Intervention(s)	CT- or MRI-guided percutaneous cryoablation
Comparator	None
Outcome measures	Overall survival Cancer-specific survival Metastasis-free survival Distant recurrence
Number of participants	n=53 (85 tumours) treated over 68 sessions
Follow-up frequency	Standard institutional protocols used.
Duration of follow-up	Mean follow-up 30.4 months (SD±22.2)
Loss to follow-up	Not reported
Methods of analysis	Outcomes were evaluated from the time of treatment to the time of event using Kaplan-Meier curves. Survival rates and corresponding 95% confidence intervals were reported.
Additional comments	None

Characteristics

Study-level characteristics

Characteristic	Study (N = 53)
% Female Sample size	n = 23 ; % = 43.4
Mean age (SD) Range	23 to 59
eGFR at baseline (ml/min/1.73 m²) Mean (SD)	88.4 (44.7)
Ethnicity - Caucasian Sample size	n = 52 ; % = 98.1
Ethnicity - Asian Sample size	n = 1 ; % = 1.9
Type of hereditary disease - VHL Sample size	n = 41 ; % = 77.4
Type of hereditary disease - HLRCC Sample size	n = 1 ; % = 1.9
Type of hereditary disease - HPRC Sample size	n = 2 ; % = 3.8
Type of hereditary disease - BHD Sample size	n = 9 ; % = 17
Solitary kidney - No Sample size	n = 44 ; % = 83
Solitary kidney - Yes Sample size	n = 9 ; % = 17
Number of tumours per patient Mean (SD)	1.6 (1)
Size of tumour (cm) Mean (SD)	2.46 (1)

Characteristic	Study (N = 53)
Previous surgery on the same kidney - Partial nephrectomy Sample size	n = 15 ; % = 28
Previous surgery on the same kidney - Percutaneous cryoablation Sample size	n = 14 ; % = 26
Previous surgery on the same kidney - Radiofrequency ablation Sample size	n = 7 ; % = 13
Previous surgery on the contralateral kidney - Radical nephrectomy Sample size	n = 8 ; % = 15
Previous surgery on the contralateral kidney - Partial nephrectomy Sample size	n = 10 ; % = 19
Previous surgery on the contralateral kidney - Radiofrequency ablation Sample size	n = 3 ; % = 6
Previous surgery on the contralateral kidney - Irreversible electroporation Sample size	n = 2 ; % = 4
Previous surgery on the contralateral kidney - Percutaneous cryoablation Sample size	n = 12 ; % = 23

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	Moderate *(Serious concerns around study design)*
Overall Risk of Bias	Applicability	Directly applicable

Park, 2010

Bibliographic Reference	Park, Byung Kwan; Kim, Chan Kyo; Percutaneous radio frequency ablation of renal tumors in patients with von Hippel-Lindau disease: preliminary results.; The Journal of urology; 2010; vol. 183 (no. 5); 1703-7

Study details

Study type	Case series
Study location	Korea
Study setting	Hospital
Study dates	October 2005 to April 2009
Sources of funding	Not reported
Inclusion criteria	People with VHL A family history of VHL AND only 1 hemangioblastoma OR visceral lesion OR 2 or more hemangioblastomas OR 1 hemangioblastoma and a visceral lesion existed. People treated with radiofrequency ablation People with renal tumour 1) a nonfatty solid tumour, which was enhanced 20 HU or more after intravenous contrast administration 2) a Bosniak category III or IV cystic tumour
Intervention(s)	Image-guided radiofrequency ablation
Comparator	None
Outcome measures	New-onset CKD
Number of participants	n=11 (48 tumours - these included 26 solid and 15 cystic tumours - one participant did not have any solid tumours)
Follow-up frequency	Follow-up imaging included unenhanced-and contrast-enhanced CT done at 1-, 6- and 12-months during year 1 after ablation, every 6 months during year 2, and every 12 months from year 3.
Duration of follow-up	6 to 40 months (mean 23 months ± 12)
Loss to follow-up	Not reported
Methods of analysis	NA
Additional comments	Two residual tumours were treated with nephrectomy. The article states that 1 tumour was treated with chemotherapy due to pulmonary metastasis, however, it was not clear whether this participant entered the study with metastasis or developed metastatic disease after treatment.

Characteristics

Study-level characteristics

Characteristic	Study (N = 11)
% Female Sample size	n = 4 ; % = 36
Mean age (SD) Mean (SD)	37.5 (9.5)
eGFR at baseline (ml/min) Mean (SD)	89.7 (23.9)
Size of solid tumours (cm) 48 tumours Range	0.8 to 5.9
Size of solid tumours (cm) 48 tumours Mean (SD)	2.3 (1.2)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design, and lack of reporting around competing interests and sources of support. It was also unclear whether participants entered with metastatic disease or developed metastatic disease at follow-up.)*
Overall Risk of Bias	Applicability	Partially directly applicable *(Unclear whether all participants had non-metastatic disease at baseline. One participant also only presented with cystic tumours and no solid tumours.)*

Ploussard, 2007

Bibliographic Reference	Ploussard, Guillaume; Droupy, Stephane; Ferlicot, Sophie; Ples, Racula; Rocher, Laurence; Richard, Stephane; Benoit, Gerard; Local recurrence after nephron-sparing surgery in von Hippel-Lindau disease.; Urology; 2007; vol. 70 (no. 3); 435-9

Study details

Study type	Case series

Study location	France
Study setting	Not reported
Study dates	February 1987 to August 2005
Sources of funding	Not reported
Inclusion criteria	People with VHL People with renal tumour
Intervention(s)	Unilateral nephron-sparing surgery Bilateral nephron-sparing surgery Nephron-sparing surgery and contralateral radical nephrectomy Bilateral radical nephrectomy
Comparator	None
Outcome measures	Cancer-specific survival Distant recurrence Need for dialysis or renal transplant
Number of participants	Partial nephrectomy n=13 (27 procedures) Partial nephrectomy and contralateral radical nephrectomy OR bilateral radical nephrectomy n=5 (6 procedures) [Data not extracted as groups could not be separated] Active surveillance n=3
Follow-up frequency	Participants underwent close surveillance with physical examination, CT, and serum creatinine determination every 6 months.
Duration of follow-up	Median follow-up 100 months (range 7 to 223)
Loss to follow-up	Not reported
Methods of analysis	NA
Additional comments	• The indication for surgical resection was a lesion larger than 30 mm with solid or mixed component. • Radical nephrectomy was necessary for tumours larger than 7 cm and/or when multifocal disease prevented the preservation of sufficient renal parenchyma. • 16 participants had a typical family history of VHL and 5 had no family history. A germline mutation was identified in all but one case.

	• Outcomes could not be extracted for bilateral radical nephrectomy and NSS and contralateral radical nephrectomy as they were not reported separately for the two groups.

Characteristics

Study-level characteristics

Characteristic	Study (N = 21)
% Female Sample size	n = 6 ; % = 29
Mean age (SD) Range	24 to 69
Mean age (SD) Mean (SD)	38.5 (*NR*)
Number of lesions per kidney Range	1 to 10
Number of lesions per kidney Mean (SD)	3.35 (*NR*)
Serum Creatinine (mg/dL) Range	0.8 to 1.8
Serum Creatinine (mg/dL) Mean (SD)	0.96 (*NR*)

Arm-level characteristics

Characteristic	Partial nephrectomy (N = 13)	Active surveillance (N = 3)
Tumour diameter (mm) Range	22 to 59	*NR*
Tumour diameter (mm) Mean (SD)	33.2 (9.2)	*NR*

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design and lack of reporting around competing interests and sources of support)*
Overall Risk of Bias	Applicability	Directly applicable

Schuhmacher, 2019

Bibliographic Reference	Schuhmacher, Patrick; Kim, Emily; Hahn, Felix; Sekula, Peggy; Jilg, Cordula Annette; Leiber, Christian; Neumann, Hartmut P; Schultze-Seemann, Wolfgang; Walz, Gerd; Zschiedrich, Stefan; Growth characteristics and therapeutic decision markers in von Hippel-Lindau disease patients with renal cell carcinoma.; Orphanet journal of rare diseases; 2019; vol. 14 (no. 1); 235

Study details

Study type	Case series
Study location	Germany
Study setting	University Medical Center
Study dates	January 2001 to January 2016
Sources of funding	Report states “not applicable”
Inclusion criteria	People with VHL People with radiologically detected ccRCC People with a minimum of 3 consecutive MRIs performed with no greater gap than 3 years
Intervention(s)	Active surveillance Partial nephrectomy
Comparator	None
Outcome measures	Distant recurrence
Number of participants	n=41 41 participants with 102 tumours were monitored; of these, 17 participants received partial nephrectomy of 40 ccRCCs.
Follow-up frequency	Not reported

Duration of follow-up	Mean 52.2 months (range 18 to 149 months)
Loss to follow-up	Not reported
Methods of analysis	NA
Additional comments	The threshold to surgery was 4 cm maximum

Characteristics

Study-level characteristics

Characteristic	**Study (N = 41)**
% Female Sample size	n = 24 ; % = 59
Mean age (SD) Range	20 to 72
Mean age (SD) Mean (SD)	35.6 (*NR*)
Number of tumours per patient Range	1 to 10
Tumour size (cm^3) Mean (SD)	4.47 (*NR*)
Tumour size - Tumours removed by partial nephrectomy Mean (SD)	41.3 (*NR*)

Quality appraisal and risk of bias – IHE checklist

Section	**Question**	**Answer**
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design and lack of reporting around participant characteristics in the partial nephrectomy participants, and details of the interventions such as frequency of imaging.)*
Overall Risk of Bias	Applicability	Directly applicable

1 Shinohara, 1995

Bibliographic Reference	Shinohara, N; Nonomura, K; Harabayashi, T; Togashi, M; Nagamori, S; Koyanagi, T; Nephron sparing surgery for renal cell carcinoma in von Hippel-Lindau disease.; The Journal of urology; 1995; vol. 154 (no. 6); 2016-9

2

3 Study details

Study type	Case series
Study location	Japan
Study setting	Not reported
Study dates	1988 to 1991
Sources of funding	Not reported
Inclusion criteria	People with renal cell carcinoma Diagnosis of RCC was initially made by excretory urography, ultrasonography and CT of the abdomen. People from families with VHL
Exclusion criteria	People with advanced renal cell carcinoma
Intervention(s)	Nephron-sparing surgery
Comparator	None
Outcome measures	Distant recurrence Need for dialysis or renal transplant
Number of participants	n=5 (33 tumours were resected)
Follow-up frequency	Serial abdominal and pelvic CT scans were performed at 3- to 6-month intervals after surgery
Duration of follow-up	Median follow-up was 61 months (range 40 to 82)
Loss to follow-up	Not reported
Methods of analysis	NA
Additional comments	4 participants treated with bilateral nephron sparing surgery underwent renal operations. Participants were taken from 3 families.

4

Characteristics

Study-level characteristics

Characteristic	Study (N = 5)
% Female Sample size	n = 4 ; % = 80
Mean age (SD) Range	35 to 60
Mean age (SD) Median (IQR)	36 (*NR* to *NR*)
Maximum tumour size (cm) Range	3 to 7.5
Tumour stage - T2 Sample size	n = 4 ; % = 80
Tumour stage - T3a Sample size	n = 1 ; % = 20
Tumour histological grade - Grade 1 Sample size	n = 2 ; % = 40
Tumour histological grade - Grade 2 Sample size	n = 3 ; % = 60
Serum Creatinine (mg/dL) Range	0.4 to 0.7
Serum Creatinine (mg/dL) Mean (SD)	0.5 (*NR*)

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design and unclear reporting around adverse events, competing interests and sources of support.)*
Overall Risk of Bias	Applicability	Directly applicable

Steinbach, 1995

Bibliographic Reference	Steinbach, F; Novick, A C; Zincke, H; Miller, D P; Williams, R D; Lund, G; Skinner, D G; Esrig, D; Richie, J P; deKernion, J B; Treatment of renal cell carcinoma in von Hippel-Lindau disease: a multicenter study.; The Journal of urology; 1995; vol. 153 (no. 6); 1812-6

Study details

Study type	Case series
Study location	The US
Study setting	8 medical centres
Study dates	Before 1993
Sources of funding	Deutsche Krebschilfe
Inclusion criteria	People with VHL Diagnosed by the presence of renal cell carcinoma and a known family history of von Hippel-Lindau disease OR by the presence of renal cell carcinoma and l other major manifestation of VHL. People who had surgery for RCC
Intervention(s)	Radical nephrectomy Nephron sparing surgery
Comparator	None
Outcome measures	Cancer-specific survival Distant recurrence New-onset CKD
Number of participants	Radical nephrectomy (n=16) - 8 participants underwent unilateral and 8 underwent bilateral radical nephrectomy Partial nephrectomy (n=49) - 8 participants underwent unilateral nephron-sparing surgery, 19 participants underwent bilateral partial nephrectomy, 22 participants underwent unilateral together with contralateral nephrectomy

Follow-up frequency	Article describes that all participants were evaluated at regular intervals with a physical examination, renal function tests, chest radiography, and abdominal CT or ultrasonography.
Duration of follow-up	Mean 68 ± 51 months
Loss to follow-up	Not reported
Methods of analysis	Cancer-specific survival rates were determined by the Kaplan-Meier method.
Additional comments	1 participant in the radical nephrectomy group had metastatic disease. Mean follow-up was significantly longer for participants with local recurrence than those who were tumour free (99±50 months vs 41±28 months).

Characteristics

Study-level characteristics

Characteristic	**Study (N = 65)**
% Female Sample size	n = 26 ; % = 40
Mean age (SD) (years) Mean (SD)	36 (11)
Serum Creatinine (mg/dL) Mean (SD)	1 (0.3)
Tumour stage - Stage I Sample size	n = 47 ; % = 75
Tumour stage - Stage II Sample size	n = 11 ; % = 17
Tumour stage - Stage III Sample size	n = 4 ; % = 6
Tumour stage - Stage IV Sample size	n = 1 ; % = 2

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design, and lack of reporting around tumour characteristics, adverse events, and competing interests.)*
Overall Risk of Bias	Applicability	Partially directly applicable *(1 participant in the radical nephrectomy group had metastatic disease.)*

Wessendorf, 2021

Bibliographic Reference	Wessendorf, Joel; Konig, Alexander; Heers, Hendrik; Mahnken, Andreas H; Repeat Percutaneous Radiofrequency Ablation of T1 Renal Cell Carcinomas is Safe in Patients with Von Hippel-Lindau Disease.; Cardiovascular and interventional radiology; 2021; vol. 44 (no. 12); 2022-2025

Study details

Study type	Case series
Study location	Germany
Study setting	Tertiary referral centre
Study dates	Not reported
Sources of funding	Study not supported by any funding. Open access funding from Projekt DEAL.
Inclusion criteria	People with VHL People who underwent radiofrequency ablation for RCCs Tumour growth > 0.5cm/year or a tumour diameter > 3 cm
Intervention(s)	Percutaneous radiofrequency ablation with non-fluoroscopic CT-guidance using posterolateral approach
Comparator	None
Outcome measures	Overall survival Need for dialysis or renal transplant
Number of participants	n=9 (21 RCCs treated with 18 procedures)
Follow-up frequency	Follow-up imaging including contrast-enhanced CT or MRI 4 to 6 months after every ablation and every 6 months thereafter.
Duration of follow-up	34.0 ± 18.1 months (0 to 58 months)
Loss to follow-up	One participant was excluded from analysis of functional outcomes due to missing data

Methods of analysis	NA
Additional comments	None

Characteristics

Study-level characteristics

Characteristic	Study (N = 9)
% Female Sample size	n = 5 ; % = 56
Mean age (SD) Mean (SD)	47.9 (10.7)
eGFR at baseline Mean (SD)	65.7 (20.7)
Previous surgery Sample size	n = 9 ; % = 100
Previous surgery - Nephron-sparing surgery Sample size	n = 6 ; % = 67
Previous surgery - Radical nephrectomy Sample size	n = 1 ; % = 11
Tumour stage 21 RCCs Sample size	n = 21 ; % = 100
Tumour stage - cT1a Sample size	n = 16 ; % = 76
Tumour stage - cT1b Sample size	n = 5 ; % = 24
Largest tumour diameter (mm) Mean (SD)	32.9 (8.6)
Chronic kidney disease Sample size	n = 3 ; % = 33

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	Moderate *(Some concerns around study design)*

Section	Question	Answer
Overall Risk of Bias	Applicability	Directly applicable

Yang, 2013

Bibliographic Reference	Yang, Bo; Autorino, Riccardo; Remer, Erick M; Laydner, Humberto K; Hillyer, Shahab; Altunrende, Fatih; White, Michael A; Khanna, Rakesh; Stein, Robert J; Haber, Georges-Pascal; O'Malley, Charles M; Kaouk, Jihad H; Probe ablation as salvage therapy for renal tumors in von Hippel-Lindau patients: the Cleveland Clinic experience with 3 years follow-up.; Urologic oncology; 2013; vol. 31 (no. 5); 686-92

Study details

Study type	Case series
Study location	The US
Study setting	Cleveland Clinic
Study dates	March 2003 to January 2010
Sources of funding	Not reported
Inclusion criteria	People with VHL Diagnosed by the presence of bilateral RCC and positive family history People who underwent 1 or more salvage ablation
Intervention(s)	Percutaneous cryoablation (13 procedures) Radiofrequency ablation (14 procedures) Laparoscopic cryoablation (3 procedures) Choice of laparoscopic or percutaneous approach was mainly based on tumour location Treatment was described as salvage therapy
Outcome measures	Overall survival Cancer-specific survival Distant recurrence Need for dialysis or renal transplant
Number of participants	n=14 (33 tumours)
Follow-up frequency	CT or MRI was performed postoperatively on day 1, then 3, 6, and 12 months and then annually thereafter.
Duration of follow-up	Mean follow-up 37.6 months (range 12 to 82 months)
Loss to follow-up	Not reported

Methods of analysis	NA
Additional comments	None

Characteristics

Study-level characteristics

Characteristic	Study (N = 14)
% Female Sample size	n = 6 ; % = 43
Mean age (SD) Range	36 to 72
Mean age (SD) Mean (SD)	45 (*NR*)
eGFR at baseline (ml/min) Mean (SD)	61 (*NR*)
Maximal renal lesion diameter (cm) Mean (SD)	2.64 (1)
Past surgical history - Radical nephrectomy Sample size	n = 12 ; % = 86
Past surgical history - Ipsilateral partial nephrectomy Sample size	n = 14 ; % = 100
Tumour location 33 tumours Sample size	n = 33 ; % = 100
Tumour location - Upper pole Sample size	n = 12 ; % = 36
Tumour location - Mid pole Sample size	n = 8 ; % = 24
Tumour location - Lower pole Sample size	n = 13 ; % = 39

Quality appraisal and risk of bias – IHE checklist

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	High *(Serious concerns around study design and lack of reporting around competing interests and sources of support.)*
Overall Risk of Bias	Applicability	Directly applicable

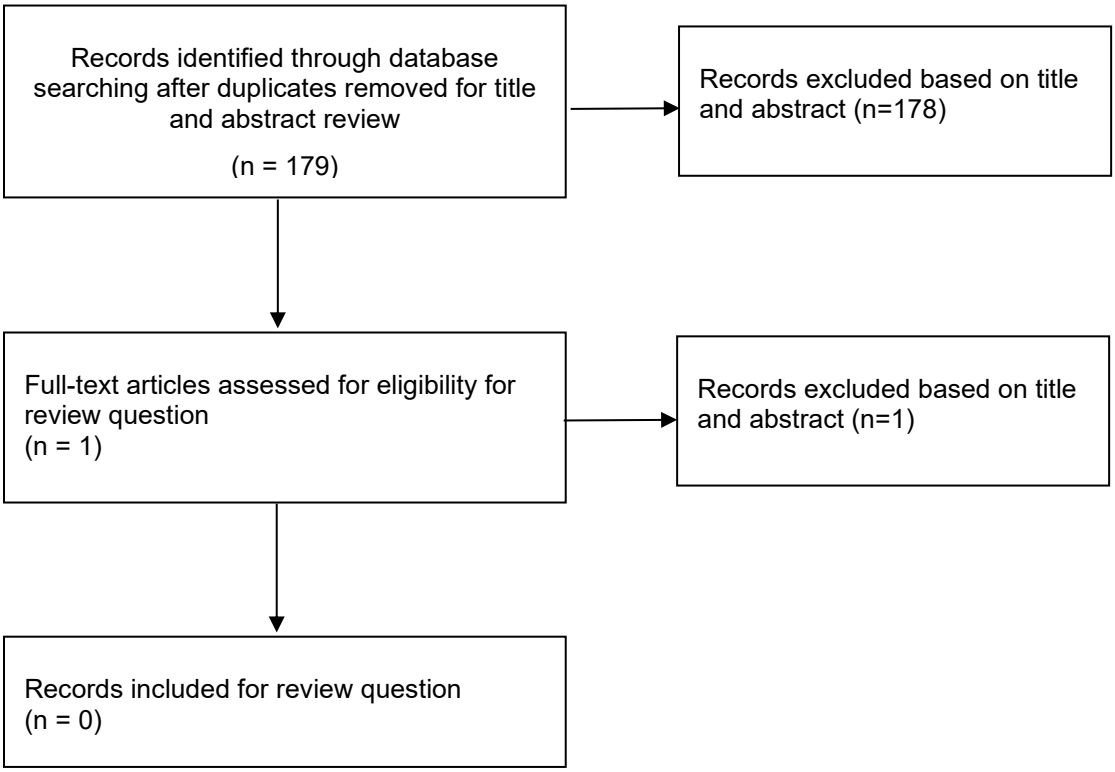
Appendix E – Forest plots

It was not possible to pool data as all evidence was non-comparative.

Appendix F – GRADE tables

It was not possible to conduct GRADE as all evidence was non-comparative.

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was identified for this review question.

Appendix I – Health economic model

No original economic modelling was conducted for this review question.

Appendix J – Excluded studies

Table 20: Excluded effectiveness studies

Study	Reason for exclusion
Anari, Pouria Yazdian, Lay, Nathan, Gopal, Nikhil et al. (2022) An MRI-based radiomics model to predict clear cell renal cell carcinoma growth rate classes in patients with von Hippel-Lindau syndrome. Abdominal radiology (New York) 47(10): 3554-3562	- Does not report an outcome of interest
Ball, Mark W, An, Julie Y, Gomella, Patrick T et al. (2020) Growth Rates of Genetically Defined Renal Tumors: Implications for Active Surveillance and Intervention. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 38(11): 1146-1153	- Does not report an outcome of interest
Benusiglio, Patrick R, Giraud, Sophie, Deveaux, Sophie et al. (2014) Renal cell tumour characteristics in patients with the Birt-Hogg-Dube cancer susceptibility syndrome: a retrospective, multicentre study. Orphanet journal of rare diseases 9: 163	- Outcomes not reported separately for different interventions
Carrion, Diego M, Linares-Espinos, Estefania, Rios Gonzalez, Emilio et al. (2020) Invasive management of renal cell carcinoma in von Hippel-Lindau disease. Central European journal of urology 73(2): 167-172	- Outcomes not reported separately for different interventions
Chayed, Zahraa, Kristensen, Lone Kroldrup, Ousager, Lilian Bomme et al. (2021) Hereditary leiomyomatosis and renal cell carcinoma: a case series and literature review. Orphanet journal of rare diseases 16(1): 34	- Not a relevant study design *Case series of published case reports*
Chen, Jiye, Zheng, Lin, Zhang, Wei et al. (2024) Percutaneous microwave ablation on management of hereditary renal cell carcinoma in Von Hippel-Lindau disease. International journal of hyperthermia : the official journal of European Society for	- Non-OECD country

Study	Reason for exclusion
Hyperthermic Oncology, North American Hyperthermia Group 41(1): 2308079	
Choyke, P L, Pavlovich, C P, Daryanani, K D et al. (2001) Intraoperative ultrasound during renal parenchymal sparing surgery for hereditary renal cancers: a 10-year experience. The Journal of urology 165(2): 397-400	- Does not report an outcome of interest
Dagher, Julien, Kammerer-Jacquet, Solene-Florence, Brunot, Angelique et al. (2016) Wild-type VHL Clear Cell Renal Cell Carcinomas Are a Distinct Clinical and Histologic Entity: A 10-Year Follow-up. European urology focus 1(3): 284-290	- Does not contain a population of people with heritable renal cancer
del Cura, Jose L, Zabala, Rosa, Iriarte, Jose I et al. (2010) Treatment of renal tumors by percutaneous ultrasound-guided radiofrequency ablation using a multitined electrode: effectiveness and complications. European urology 57(3): 459-65	- Unclear whether participants had heritable RCC
Ellati, R.T., Abukhiran, I., Alqasem, K. et al. (2017) Clinicopathologic Features of Translocation Renal Cell Carcinoma. Clinical Genitourinary Cancer 15(1): 112	- Outcomes not reported separately for different interventions
Fahmy, Wahib, Safwat, Ahmed S, Bissada, Nabil K et al. (2007) Multiple/bilateral renal tumors in patients with Birt-Hogg-Dube syndrome. International urology and nephrology 39(4): 995-9	- Does not report an outcome of interest
Farhadi, Faraz, Nikpanah, Moozhan, Li, Xiaobai et al. (2018) Germline VHL gene variant in patients with von Hippel-Lindau disease does not predict renal tumor growth. Abdominal radiology (New York) 43(10): 2743-2749	- Does not report an outcome of interest
Gopal, Nikhil, Anari, Pouria Yazdian, Chaurasia, Aditi et al. (2024) The kidney imaging surveillance scoring system (KISSS): using qualitative MRI features to predict growth rate of renal tumors in patients with von-Hippel Lindau (VHL)	- Does not report an outcome of interest

Study	Reason for exclusion
syndrome. Abdominal radiology (New York) 49(2): 542-550	
Hakimi, A.A., Ostrovnaya, I., Reva, B. et al. (2013) Adverse outcomes in clear cell renal cell carcinoma with mutations of 3p21 epigenetic regulators BAP1 and SETD2: A report by MSKCC and the KIRC TCGA research network. Clinical Cancer Research 19(12): 3259	- Data not reported in an extractable format *Article reports hazard ratios for mutation compared to wild type*
Hankins, Ryan A, Walton-Diaz, Annerleim, Truong, Hong et al. (2016) Renal functional outcomes after robotic multiplex partial nephrectomy: the National Cancer Institute experience with robotic partial nephrectomy for 3 or more tumors in a single kidney. International urology and nephrology 48(11): 1817-1821	- Does not report an outcome of interest
Herring, J C, Enquist, E G, Chernoff, A et al. (2001) Parenchymal sparing surgery in patients with hereditary renal cell carcinoma: 10-year experience. The Journal of urology 165(3): 777-81	- Unclear how many participants underwent each intervention
Hong, Baoan, Zhang, Zhongyuan, Zhou, Jingcheng et al. (2019) Distinctive clinicopathological features of Von Hippel-Lindau-associated hereditary renal cell carcinoma: A single-institution study. Oncology letters 17(5): 4600-4606	- Non-OECD country
Hwang, J J, Walther, M M, Pautler, S E et al. (2004) Radio frequency ablation of small renal tumors:: intermediate results. The Journal of urology 171(5): 1814-8	- Does not report an outcome of interest
Jilg, C A, Neumann, H P, Glasker, S et al. (2012) Growth kinetics in von Hippel-Lindau-associated renal cell carcinoma. Urologia internationalis 88(1): 71-8	- Outcomes not reported separately for different interventions
Jilg, C A, Neumann, Hartmut P H, Glasker, S et al. (2012) Nephron sparing surgery in von Hippel-Lindau associated renal cell carcinoma; clinicopathological long-term follow-up. Familial cancer 11(3): 387-94	- Outcomes not reported separately for different interventions

Study	Reason for exclusion
Joly, Dominique, Mejean, Arnaud, Correas, Jean-Michel et al. (2011) Progress in nephron sparing therapy for renal cell carcinoma and von Hippel-Lindau disease. The Journal of urology 185(6): 2056-60	- Outcomes not reported separately for different interventions
Jonasch, E., Balijepalli, C., Yan, K. et al. (2024) Efficacy, Effectiveness, and Safety of Interventions for Von Hippel-Lindau Associated Renal Cell Carcinoma: A Systematic Literature Review. Kidney Cancer 8(1): 1	- Systematic review source of primary study references
Kamboj, M., Gupta, G., Pasricha, S. et al. (2024) Fumarate hydratase-deficient renal cell carcinoma: an oncology care institutional experience. APMIS 132(8): 544	- Population included a high proportion of participants with metastatic disease
Li, F.P., Decker, H.-J.H., Zbar, B. et al. (1993) Clinical and genetic studies of renal cell carcinomas in a family with a constitutional chromosome 3;8 translocation: Genetics of familial renal carcinoma. Annals of Internal Medicine 118(2): 106	- Outcomes not reported separately for different interventions
Li, Ziao, Zhang, Jin, Zhang, Lei et al. (2021) Natural history and growth kinetics of clear cell renal cell carcinoma in sporadic and von Hippel-Lindau disease. Translational andrology and urology 10(3): 1064-1070	- Does not report an outcome of interest
Matin, Surena F, Ahrar, Kamran, Wood, Christopher G et al. (2008) Patterns of intervention for renal lesions in von Hippel-Lindau disease. BJU international 102(8): 940-5	- Outcomes not reported separately for different interventions
Park, Sung Yoon, Park, Byung Kwan, Kim, Chan Kyo et al. (2011) Percutaneous radiofrequency ablation of renal cell carcinomas in patients with von Hippel Lindau disease previously undergoing a radical nephrectomy or repeated nephron-sparing surgery. Acta radiologica (Stockholm, Sweden : 1987) 52(6): 680-5	- Does not report an outcome of interest

Study	Reason for exclusion
Pavlovich, C.P., Grubb III, R.L., Hurley, K. et al. (2005) Evaluation and management of renal tumors in the Birt-Hogg-Dube syndrome. Journal of Urology 173(5): 1482	- Unclear how many participants had metastatic disease at baseline
Peng, Xiang, Chen, Jinchao, Wang, Jiangyi et al. (2019) Natural history of renal tumours in von Hippel-Lindau disease: a large retrospective study of Chinese patients. Journal of medical genetics 56(6): 380-387	- Outcomes not reported separately for different interventions
Persad, R A, Probert, J L, Sharma, S D et al. (1997) Surgical management of the renal manifestations of von Hippel-Lindau disease: a review of a United Kingdom case series. British journal of urology 80(3): 392-6	- Unclear how many participants had metastatic disease at baseline
Pomerri, Fabio, Opocher, Giuseppe, Dal Bosco, Chiara et al. (2015) Optimal follow-up intervals in active surveillance of renal masses in patients with von Hippel-Lindau disease. European radiology 25(7): 2025-32	- Population included people without RCC
Roupret, Morgan, Hopirtean, Vincent, Mejean, Arnaud et al. (2003) Nephron sparing surgery for renal cell carcinoma and von Hippel-Lindau's disease: a single center experience. The Journal of urology 170(5): 1752-5	- Unclear how many participants underwent each intervention
Salome, F, Colombeau, P, Fermeaux, V et al. (1998) Renal lesions in Von Hippel-Lindau disease: the benign, the malignant, the unknown. European urology 34(5): 383-92	- Population included people without RCC
Shingleton, W.B. and Sewell Jr., P.E. (2002) Percutaneous renal cryoablation of renal tumors in patients with von Hippel-Lindau disease. Journal of Urology 167(3): 1268	- Does not report an outcome of interest
Siegel, C. (2012) Re: Incidence of multiple sporadic renal cell carcinomas in patients referred for renal radiofrequency ablation: Implications for imaging follow-up. Journal of Urology 187(4): 1225	- Editorial comment

Study	Reason for exclusion
Singer, Eric A, Vourganti, Srinivas, Lin, Kelly Y et al. (2012) Outcomes of patients with surgically treated bilateral renal masses and a minimum of 10 years of followup. The Journal of urology 188(6): 2084-8	- Outcomes not reported separately for different interventions
Singh, S., Dehghani Firouzabadi, F., Chaurasia, A. et al. (2024) CT-derived radiomics predict the growth rate of renal tumours in von Hippel-Lindau syndrome. Clinical Radiology 79(5): e675	- Does not report an outcome of interest
Thompson, Alexander J, Alwan, Yousef M, Ramani, Vijay A C et al. (2023) Cost-effectiveness model of renal cell carcinoma (RCC) surveillance in hereditary leiomyomatosis and renal cell carcinoma (HLRCC). Journal of medical genetics 60(1): 41-47	- Does not report an outcome of interest
Walther, M M, Choyke, P L, Glenn, G et al. (1999) Renal cancer in families with hereditary renal cancer: prospective analysis of a tumor size threshold for renal parenchymal sparing surgery. The Journal of urology 161(5): 1475-9	- Suitable outcome only reported for a subset of the population
Walther, M M, Choyke, P L, Weiss, G et al. (1995) Parenchymal sparing surgery in patients with hereditary renal cell carcinoma. The Journal of urology 153(3pt2): 913-6	- Unclear how many participants underwent each intervention
Wang, Jie, Zhang, Lei, Qiu, Jianhui et al. (2022) Natural history of Von Hippel-Lindau disease-associated and sporadic clear cell renal cell carcinoma: a comparative study. Journal of cancer research and clinical oncology 148(10): 2631-2641	- Does not report an outcome of interest
Yu, Y., Zheng, M., Zhu, W. et al. (2021) Hereditary leiomyomatosis and renal cell cancer (HLRCC): Case series and review of the literature. Urologic Oncology: Seminars and Original Investigations 39(11): 791e9	- Does not report an outcome of interest *Metastasis outcome not reported for case 3*
Zhang, J., Huang, Y.-R., Liu, D.-M. et al. (2007) Management of solid renal tumour	- Non-OECD country

Study	Reason for exclusion
associated with von Hippel-Lindau disease. Chinese Medical Journal 120(22): 2049	
Zhang, Jin, Pan, Jia-Hua, Dong, Bai-Jun et al. (2012) Active surveillance of renal masses in von Hippel-Lindau disease: growth rates and clinical outcome over a median follow-up period of 56 months. Familial cancer 11(2): 209-14	- Non-OECD country

Economic references excluded at full text (n = 1)

Table 21: Excluded economic studies

Study	Reason for exclusion
Thompson, Alexander J, Alwan, Yousef M, Ramani, Vijay A C et al. (2023) Cost-effectiveness model of renal cell carcinoma (RCC) surveillance in hereditary leiomyomatosis and renal cell carcinoma (HLRCC). Journal of medical genetics 60(1): 41-47	- Population did not have suspected or confirmed RCC