National Institute for Health and Care Excellence

Kidney cancer: diagnosis and management

[H] Evidence review for management of advanced renal cell carcinoma using non-pharmacological interventions

NICE guideline NG256

Evidence underpinning recommendations 1.12.1 to 1.12.2 and 1.14.1 to 1.14.8, and research recommendations in the NICE guideline

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Contents

1 Management of advanced renal cell carcinoma using non-pharmacological interventions before systemic anti-cancer therapy

1.1 Review question

What is the clinical and cost-effectiveness of non-pharmacological interventions used before systemic anti-cancer therapy for adults with advanced renal cell carcinoma?

1.1.1 Introduction

There are number of treatment options available for advanced renal cell carcinoma. These usually include pharmacological (systemic anti-cancer therapy, SACT) and non-pharmacological interventions. It is important to understand where non-pharmacological treatment modalities could be considered alongside SACT for reducing disease burden and improving survival benefits in the most effective manner.

Therefore, this review aims to evaluate the clinical and cost-effectiveness of non-pharmacological interventions before initial treatment with SACT in managing advanced renal cell carcinoma. Review H2 assesses the clinical and cost-effectiveness of non-pharmacological interventions after SACT.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	Adults (18 years or over) with advanced RCC* who have not previously received systemic anti-cancer treatment (SACT). *defined as metastatic/ advanced RCC or locally advanced inoperable RCC (histologically confirmed or suspected on imaging). Advanced RCC diagnosis confirmed according to the clinical or pathological TNM classification Exclusion: • Adults with localised or locally advanced disease that is considered to be operable. • Adults with advanced disease who are having palliative care only.

Interventions	• Non-pharmacological procedures carried out before SACT to manage primary mass:
	  ○ Cytoreductive nephrectomy
	  ○ Stereotactic ablative radiotherapy (SABR)
	• Managing metastases:

	○ Surgical removal ○ Thermal ablation: ▪ Radiofrequency ablation ▪ Cryotherapy ▪ Microwave ablation ○ Radiotherapy: ▪ External beam radiotherapy (EBRT) ▪ Stereotactic ablative radiotherapy (SABR)
Comparator	No non-pharmacological intervention before SACT (no delayed SACT): • SACT without a non-pharmacological intervention • SACT followed by an included non-pharmacological intervention
Outcomes	• Progression-free survival • Overall survival or if not reported: ○ Mortality • Cancer-specific survival or if not reported: ○ Cancer-specific mortality • Severe adverse events reported as: ○ observed in the intraoperative period ○ observed in postoperative period • Duration of hospital stay • Quality of life
Study type	• Randomised controlled trials (RCTs) • Any controlled, non-randomised studies • Cohort studies (prospective and retrospective observational studies) • Systematic reviews of the above studies

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.

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

1. Mortality at timepoints of 90 days or less was not included in this review. This was considered to be within the postoperative period and therefore covered by the outcome of postoperative severe adverse events (PSAE). PSAE was required to be reported using the acceptable classifications - Clavien-Dindo classification or Common Terminology Criteria for Adverse Events (CTCAE) in order to be included.

2. Where more than 1 timepoint was reported we reported data at up to 5 years and 5 to 10 years. Where several time points were reported that could fit in the same category, the latest time point was used.

3. For outcomes where the line of no effect was defined as the minimal important difference (MID), a power calculation from a robust RCT (Mejean et al. 2018, included in this review) was used to determine the minimum sample size needed for consideration for the second downgrade criteria for the imprecision domain in GRADE. For all outcomes in this review, a sample size of less than 576 was used for downgrading.

4. Important confounders considered for assessing the quality of the included studies under this review were discussed and agreed with the committee. These confounders were:

    - Age
    - TNM classification
    - Primary RCC type e.g. clear cell, papillary and chromophobe
    - Tumour grade
    - Renal function at baseline
    - Performance status of participants at baseline
    - Location and number of metastases

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 18/01/2024 and re-run on 14/02/2025. The following databases were searched: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), Epistemonikos (Epistemonikos) and MEDLINE ALL (Ovid). Limits were applied to remove animal studies, conference abstracts, editorials, letters, news items and commentaries, as well as papers not published in the English language. Filters were used to limit to OECD countries, systematic reviews, randomised controlled trials and observational studies.

The searches for the cost effectiveness evidence were run between 05/01/2024 and 07/01/2024 and re-run on 06/05/2025. The following databases were searched: EconLit (Ovid), Embase (Ovid), HTA (CRD), International HTA database (INAHTA), MEDLINE ALL (Ovid) and NHS Economic Evaluations Database (CRD). Limits were applied to remove animal studies, conference abstracts, editorials, letters, news items and commentaries, as well as papers not published in the English language. Filters were used to limit to OECD countries and cost utility 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. Severe adverse event classifications were further specified:

    - The Intraoperative Adverse Incident Classification (EAUiaiC) and Clavien-Dindo Classification, both of which were already specified in the protocol, were used for thermal ablation and surgery interventions only.

- The Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 was added to the protocol to be used for SABR and EBRT interventions, or for comparisons where one arm was SACT only. This addition aligns this protocol with others in this guideline (reviews A, B and C) and reflects the fact that Clavien-Dindo is usually used for surgery.

2. The quality of life outcomes were extracted when measured using EORTC Core Quality of Life Questionnaire and EuroQol-5 dimensions (EQ-5D). Later in the process it was agreed to include two additional scales assessing the quality of life outcomes as these are specific to advanced RCC. These two additional scales were:

    - Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index (FKSI: both the FKSI-15 and the FKSI-DRS)

    - Renal Cell Carcinoma Symptom Index (RCC-SI)

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A single systematic search was carried out to identify potentially relevant studies for the current review (parts H1 and H2) and reviews A, B and C (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). This search found 19,882 references (see appendix B for the literature search strategy).

These 19,882 references were screened at title and abstract level against the review protocols, with 19,208 excluded at this level. 176 articles were assessed at full text for review H (H1 and H2 combined) (the remainder of those not excluded at title and abstract were assessed at full text stage for review A, B or C). 10% of references were screened separately by two reviewers with 99.9% agreement. Discrepancies were resolved by discussion.

The full texts of 176 references were ordered for closer inspection. A total of 27 articles – five RCTs and 22 retrospective cohort studies – met the criteria specified in the review protocol for review H1 (appendix A). Eighteen studies compared upfront cytoreductive nephrectomy (cytoreductive nephrectomy before systemic anti-cancer therapy [SACT]) with SACT alone, and 15 studies compared upfront cytoreductive nephrectomy with deferred cytoreductive nephrectomy (cytoreductive nephrectomy after SACT).

For a summary of the 27 articles included in this review see Table 2.

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

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 characteristics of the included randomised controlled trials

Study details	Population	Intervention	Comparator	Outcomes	Risk of bias
Bex (2019) SURTIME (NCT01099423) Multicentre study with 19 institutions in the Netherlands, Belgium, the United Kingdom, and Canada Study dates: This randomised clinical trial began on July 14, 2010, and continued until March 24, 2016, with a median follow-up of 3.3 years (range, 0-6.2 years) and a clinical cutoff date for this report of May 5, 2017	N = 99 People aged 18 years or older, histologically confirmed, previously untreated clear cell metastatic renal cell carcinoma, resectable asymptomatic primary tumour in situ, required therapy with sunitinib, a life expectancy greater than 3 months, adequate bone marrow, liver, cardiac, and renal function, and 3 or fewer surgical risk factors Key exclusion criteria: not reported	Immediate cytoreductive nephrectomy + sunitinib (n = 50)	Deferred cytoreductive nephrectomy + sunitinib (n = 49)	• Overall survival • Progression-free survival	Moderate
De Bruijn (2019) SURTIME (NCT01099423) Multicentre study with 19 institutions in the Netherlands,	N = 99 People aged 18 years or older, histologically confirmed, previously untreated clear cell metastatic renal cell carcinoma,	Immediate cytoreductive nephrectomy + sunitinib (n = 50)	Deferred cytoreductive nephrectomy + sunitinib (n = 49)	• Duration of hospital stay	Moderate

Study details	Population	Intervention	Comparator	Outcomes	Risk of bias
Belgium, the United Kingdom, and Canada Study dates: Began on July 14, 2010, and continued until March 24, 2016	resectable asymptomatic primary tumour in situ, required therapy with sunitinib, a life expectancy greater than 3 months, adequate bone marrow, liver, cardiac, and renal function, and 3 or fewer surgical risk factors Key exclusion criteria: not reported				
Mejean (2021) CARMENA trial - NCT00930033 Multicentre - Not reported where the centres were based Study dates: 2009 to October 2018	N = 450 Patients with clear cell renal cell carcinoma confirmed on mandatory biopsy and documented metastatic disease, Eastern Cooperative Oncology Group (ECOG) status score of 0 to 1, absence of brain metastases or treated brain metastases without recurrence 3 weeks after treatment, acceptable organ function Key exclusion criteria: Patients who received previous systemic treatment for kidney cancer (including VEGF-targeted	Cytoreductive nephrectomy + sunitinib (n = 226)	Sunitinib alone (n = 224)	• Overall survival	Moderate

Study details	Population	Intervention	Comparator	Outcomes	Risk of bias
	therapy) or anticoagulants, patients with any medical condition, including cardiovascular disease, that ruled them out as candidates for treatment				
Mejean (2018) CARMENA trial - NCT00930033 Multicentre - Not reported where the centres were based Study dates: 2009 to October 2017	N = 450 Patients with clear cell renal cell carcinoma confirmed on mandatory biopsy and documented metastatic disease, Eastern Cooperative Oncology Group (ECOG) status score of 0 to 1, absence of brain metastases or treated brain metastases without recurrence 3 weeks after treatment, acceptable organ function Key exclusion criteria: Patients who received previous systemic treatment for kidney cancer (including VEGF-targeted therapy) or anticoagulants, patients with any medical condition, including cardiovascular disease, that ruled	Cytoreductive nephrectomy + sunitinib (n = 226)	Sunitinib alone (n = 224)	• Progression-free survival • Adverse event grade ≥3 (Clavien Dindo)	Moderate

Study details	Population	Intervention	Comparator	Outcomes	Risk of bias
	them out as candidates for treatment				
Shen (2023) China Study dates: 2018 – 2020	N = 84 Histologically or cytologically confirmed clear cell renal cell carcinoma, measurable disease according to RECIST 1.1 criteria, including primary and metastatic lesions, Eastern Cooperative Oncology Group (ECOG) status score of 0 to 1, life expectancy > 24 weeks, primary resectable tumour at first diagnosis Key exclusion criteria: Brain or liver metastases, poor prognosis as defined by Memorial Sloan-Kettering Cancer Center (MSKCC) or Heng criteria, severe hepatic or renal insufficiency or uncontrolled hypertension or diabetes mellitus, active infection, primary tumours from other sites, previous surgical or systemic treatment for metastatic renal cell carcinoma	Immediate cytoreductive nephrectomy (n = 42) before PD1 inhibitor SACT (nivolumab)	Delayed cytoreductive nephrectomy (n = 42) after PD1 inhibitor SACT (nivolumab)	• Overall survival • Progression-free survival	Moderate

See appendix D for full evidence tables.

Table 3: Summary of characteristics of the included non-randomised controlled trials

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
Bakouny (2023) United States - uses the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) database Study dates: January 2020	N = 437 Initiated first-line systemic therapy on or after January 1, 2009 Diagnosed with de novo metastatic renal cell carcinoma or had not received a nephrectomy for localised renal cell carcinoma Key exclusion criteria: Missing dates of diagnosis or dates of metastatic disease Missing information on whether they had a nephrectomy or the date of nephrectomy	Immune checkpoint inhibitors with upfront cytoreductive nephrectomy (n = 234)	Immune checkpoint inhibitors no upfront cytoreductive nephrectomy (n = 203)	• Cytoreductive nephrectomy versus no cytoreductive nephrectomy • age (<65, 65–74, or >75 yr) • presence of bone, brain, or liver metastases (yes or no) • non– clear cell or sarcomatoid histology (yes or no) • Karnofsky Performance Scale (KPS: ≥80 or <80) • the number of IMDC risk factors (≤1, 2, 3, or ≥4)	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
	Missing dates of death or last follow-up					
Bhindi (2018) United States – utilises NCDB database Study dates: 2006 - 2013	N = 15,068 People with metastatic kidney cancer. Key exclusion criteria: any other carcinoma, missing data, not receiving treatment within 3 months of diagnosis.	Initial cytoreductive nephrectomy then targeted therapy (n = 6,731)	Initial targeted therapy followed by cytoreductive nephrectomy (n = 8,337)	• Age • Sex • Race • Charlson co-morbidity index • Income • Educational status • Country • Facility location • Facility type • Primary tumour histology • TNM classification	• Overall survival	Serious
Bhindi (2020) IMDC database (33 centres globally) Study dates: 2006 to 2018	N = 1,541 People receiving sunitinib as first line systemic anti-cancer therapy. Key exclusion criteria: unknown timings of	Upfront cytoreductive nephrectomy then sunitinib (n = 805)	Sunitinib followed by deferred cytoreductive nephrectomy (n = 85)	• Age • Sex • Year of diagnosis • IMDC risk, • Clear cell histology	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
	surgery, missing data, SACT after 12 months of diagnosis.		Sunitinib alone (n = 651)	• Number of metastatic sites • Location of metastases		
Chakiryan (2022) United States – utilises NCDB database Study dates: 2006 to 2016	N = 12,154 People with metastatic renal cancer with complete data.	Up-front cytoreductive nephrectomy (n = 4393) before SACT (described only as targeted therapy)	No cytoreductive nephrectomy, only systemic anti-cancer therapy alone (n = 7761) after SACT (described only as targeted therapy)	• Age • Sex • Race • Charlson-Deyo score • Year of diagnosis • Clinical staging • Cytoreductive nephrectomy status	• Overall survival	Serious
Choueiri (2011) United States and Canada Study dates: August 2004 and July 2008	N = 314 Patients diagnosed with metastatic renal cell carcinoma of any pathological subtype and treated with sunitinib, sorafenib or bevacizumab	Cytoreductive nephrectomy, before systemic anti-cancer therapy (sunitinib, sorafenib or bevacizumab) (n = 201)	No cytoreductive nephrectomy, only systemic anti-cancer therapy (sunitinib, sorafenib or bevacizumab) (n = 113)	• Patients with or without brain metastases • with Karnofsky performance status 80% or greater vs less than 80% • with more than 1 site of metastasis	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
				vs 1 site of metastasis • on different types of vascular endothelial growth factor targeted therapy		
de Groot (2016) Netherlands - Patients from the Dutch Cancer Registry Study dates: January 2008 and December 2010	N = 146 Patients diagnosed with metastatic renal cell carcinoma (i.e., metastases at initial presentation) of any histologic subtype and treated with first-line sunitinib Key exclusion criteria: Not reported	Cytoreductive nephrectomy then sunitinib (n = 73)	No cytoreductive nephrectomy, only sunitinib (n = 73)	• Baseline demographics (age at diagnosis and gender) • 3 additional clinical factors (histology, clinical tumour stage, and regional lymph node involvement)	• Overall survival	Serious
Dragomir (2022) Canada – utilises Canadian Kidney Cancer information system	N = 708 People with histologically diagnosed renal cell carcinoma.	Cytoreductive nephrectomy before systemic therapy (n = 383) Type of SACT – sunitinib (n=230), pazopanib (n=72), ipilimumab/nivolumab (n=	Cytoreductive nephrectomy after systemic therapy (n = 73)	• Age • Sex • Sites and number of organs for metastasis • Cell histology	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
Study dates: 2011 to 2020	Key exclusion criteria: People with indolent metastatic disease	3), nivolumab, everolimus / pembrolizumab / temsirolimus / atezolizumab / axitinib / lenvatinib (n= 37)	Systemic therapy only (n = 252) Type of SACT – sunitinib (n=52), pazopanib (n=8), ipilimumab / nivolumab (n= 3), nivolumab, everolimus / pembrolizumab / temsirolimus / atezolizumab / axitinib / lenvatinib (n= 10)	• IMDC risk • Charlson comorbidity index		
Ghatalia (2022) United States - uses the nationwide US Flatiron Health (FH) electronic health record (EHR)-derived deidentified database Study dates:2011 - 2020	N = 1,719 Patients with clear cell histology and synchronous metastases Key exclusion criteria: Not reported	Upfront cytoreductive nephrectomy (n = 605) Type of SACT- ipilimumab / nivolumab (n=59), Pembrolizumab / axitinib (n= 18), avelumab / axitinib (n=2), nivolumab/ pazopanib (n= 1), bevacizumab / INFa2b (n= 3), immunotherapy alone (n=33), VEGFR inhibitors	Deferred cytoreductive nephrectomy (n = 142) Systemic therapy alone (n = 972) Type of SACT - ipilimumab / nivolumab (n=17), pembrolizumab /	• Age • Gender • Race • insurance at diagnosis • IMDC risk group	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
		(n= 388), mTOR inhibitors (n= 101)	axitinib (n= 11), immunotherapy alone (n= 4), VEGFR inhibitors (n= 89), mTOR inhibitors (n= 13)			
Gunenc (2024) United States Study dates: April 2016 – October 2022	N = 51 Patients with metastatic renal cell carcinoma receiving immunotherapy-based therapies and undergoing cytoreductive nephrectomy Key exclusion: patients who did not receive immunotherapy-based therapies	Upfront cytoreductive nephrectomy (n=13): patients who were receiving immunotherapy-based therapies after surgery Type of SACT – immune checkpoint inhibitors, tyrosine kinase inhibitors (in combination or as monotherapies).	Deferred cytoreductive nephrectomy (n=38): patients who were receiving immunotherapy-based therapies in the preoperative setting Type of SACT – immune checkpoint inhibitors, tyrosine kinase inhibitors (in combination or as monotherapies).	• Not reported	• Overall survival • Progression free survival	Serious
Hara (2023) Japan - used the institutional medical	N = 54	Cytoreductive nephrectomy before ipilimumab plus nivolumab (n = 21)	Without cytoreductive nephrectomy (n = 33)	• Age • Body mass index • Sex	• Overall survival • Progression-free survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
record database at Kobe University Hospital and five affiliated hospitals Study dates: October 2018 and December 2021	Patients with synchronous metastatic renal cell carcinoma Key exclusion criteria: Patients who received deferred cytoreductive nephrectomy			• International Metastatic RCC Database Consortium risk classification • Histology • Presence of liver, brain, or bone metastasis • Clinical T stage • Neutrophil lymphocyte ratio • Number of metastasis • Presence of tumour associated symptoms		
Hatakeyama (2021) Japan - Michinoku Japan Urological Cancer Study Group database	N = 278 Patients with primary metastatic renal cell carcinoma Key exclusion criteria: Treatment with first-line	Immediate cytoreductive nephrectomy followed by first-line tyrosine kinase inhibitors (n = 107)	Deferred cytoreductive nephrectomy - after receiving tyrosine kinase inhibitors (n = 39)	• Age • Sex • Performance status • Number of IMDC risk factors	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
Study dates: January 2008 - November 2019	interferon, mammalian target of rapamycin inhibitors, immunotherapy, or chemotherapy; a period from diagnosis to first treatment of more than 3 months; a period of surveillance after immediate cytoreductive nephrectomy of more than 3 months; a follow-up period from the first treatment of less than 3 months		Systemic anti-cancer therapy alone - tyrosine kinase inhibitors (n = 132)	• Clinical stage (cT3b–4) • Number of metastatic organs		
Macleod (2018) United States - data use agreement set forth by The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program data linked with Medicare claims	N = 537 Patients with metastatic renal cell carcinoma Key exclusion criteria: Incomplete treatment claims data, under 66 years of age, patients receiving cytoreductive nephrectomy but no additional therapy, competing non-metastatic	Initial cytoreductive nephrectomy followed by targeted therapy (n = 190)	No cytoreductive nephrectomy, only initial systemic therapy (n = 347)	• Demographic factors (age, race, ethnicity, rural status) • Treatment era (first half and latter half of study period) • Cancer severity (tumour stage, nodal status, histology)	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
Study dates: 2006 – 2011	renal cell carcinoma stage IV cancer			• Comorbidity (Charlson-Klabunde index) • SEER registry		
Manley (2017) United States Study dates: 2005 - 2013	N = 123 Patients with metastatic renal cell carcinoma Key exclusion criteria: Patients with missing survival data, with incomplete clinical data and patients who received prior immunotherapy	Cytoreductive nephrectomy then targeted therapy (n = 88)	No cytoreductive nephrectomy, only targeted therapy (n = 35)	• Age • Comorbidity	• Overall survival	Serious
Meagher (2024) Italy and Spain – used data from the REMARCC database which collected data from 14 North American and European institutions	N = 189 Patients diagnosed with metastatic renal cell carcinoma who underwent cytoreductive nephrectomy	Upfront cytoreductive nephrectomy followed by systemic therapy Type of SACT – tyrosine kinase inhibitor or immunotherapy	Systemic therapy followed by deferred cytoreductive nephrectomy Type of SACT – tyrosine kinase inhibitor or immunotherapy	Not reported	• Overall survival • Cancer-specific survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
Study dates: January 2006 to October 2019						
Patel (2016) United States Study dates: July 2007 to January 2014	N = 48 Patients diagnosed with metastatic renal cell carcinoma, primary systemic therapy was offered to all patients Key exclusion criteria: Patients with overwhelming burden of metastatic disease, with poor performance status, who proceeded to systemic therapy after the initial evaluation without a plan to offer cytoreductive nephrectomy, tumour histology was not clear cell renal cell carcinoma, patients who undergone prior chemotherapy or immunotherapy	Cytoreductive nephrectomy then sunitinib (n = 27)	Sunitinib followed by cytoreductive nephrectomy (n = 21)	• Age • Race • BMI • ECOG • Type of procedure performed • Surgical approach • RENAL nephrometry score • Tumour grade • Presence of thrombus	• Duration of hospital stay • Surgical complications – Grade 3a/b (Clavien-Dindo)	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
Poprach (2020) Czech Republic - RenIS Registry database Study dates: 2007 to 2018	N = 730 Patients with synchronous metastatic disease or Key exclusion criteria: Not reported	Cytoreductive nephrectomy within 3 months of diagnosis then targeted therapies (pazopanib or sunitinib) (n = 458)	No cytoreductive nephrectomy, only targeted therapies (pazopanib or sunitinib) (n = 272)	• Not reported	• Overall survival • Progression-free survival	Serious
Singla (2020) United States - uses the National Cancer Database (NCDB) Study dates: 2015 - 2016	N = 221 Patients diagnosed with metastatic renal clear cell carcinoma Key exclusion criteria: Patients who received any non-immunotherapy systemic therapies	Cytoreductive nephrectomy then immunotherapy (n = 197)	Immunotherapy followed by cytoreductive nephrectomy (n = 24)	• Patient demographics • Performance of cytoreductive nephrectomy • Presence of sarcomatoid features • Primary tumour size • cT stage • cN stage • Presence of bone, brain, liver, or lung metastases	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
				• Number of known metastatic sites • Time to receipt of immunotherapy from diagnosis		
Stroup (2013) United States - multi-institutional (University of California San Diego Medical Centre; San Diego Veterans Administration Medical Centre; University of Tennessee Health Sciences Centre Memphis) Study dates: May 2005 to August 2009	N = 35 Patients diagnosed with metastatic renal cell carcinoma Key exclusion criteria: Patients with an overwhelming burden of metastatic disease, with poor performance status, who proceeded to systemic therapy after the initial evaluation without a plan to offer cytoreductive nephrectomy, tumour histology was not clear cell renal cell carcinoma, patients who had undergone prior chemotherapy or immunotherapy	Cytoreductive nephrectomy then sunitinib (n = 17)	Sunitinib followed by cytoreductive nephrectomy (n = 11) Sunitinib alone (n = 7)	• Age • Race • BMI • ECOG score (0 or 1 vs >1) • Tumour size (<7 vs ≥7 cm) • Tumour grade • Inferior vena cava thrombus • Number of metastatic lesions (<5 vs ≥5)	• Overall survival • Cancer specific survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
Takemura (2023) Multicentre collaboration involving participants from more than 40 institutions worldwide: Australia, Belgium, Canada, Denmark, Germany, Greece, Italy, Japan, Mexico, Netherlands, New Zealand, Singapore, South Korea, Spain, UK, and the United States Study dates: Not reported	N = 807 Patients received frontline immuno-oncology based combinations, including immuno-oncology/immuno-oncology doublet therapy and immuno-oncology/tyrosine kinase inhibitor combination therapy , patients diagnosed with either synchronous metastatic renal cell carcinoma or metachronous metastatic renal cell carcinoma without previous nephrectomy for localized renal cell carcinoma, patient did not die nor were censored within a fixed landmark time, with different landmark time periods (6, 9, 12, and 18 months) examined Key exclusion criteria: Patients with missing data	Upfront cytoreductive nephrectomy (n = 327) Immuno-oncology alone (n = 440)	Deferred cytoreductive nephrectomy (n = 40) Type of SACT – Immuno-oncolocy based combination	• Not reported	• Mortality	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
	for the date of diagnosis or metastasis, patients with missing data for whether they underwent nephrectomy, or the date of nephrectomy, patients with missing data for whether they are dead or alive, or the date of death or last follow-up					
Xu (2019) China - Department of Urology, Fudan University Shanghai Cancer Centre (FUSCC) Shanghai Study dates: May 2009 and June 2018	N = 118 Patients who had metastases on initial diagnosis and who were treated by urologists according to the standard treatment at the institution Key exclusion criteria: Not reported	Cytoreductive nephrectomy then sunitinib (n = 70)	Sunitinib alone (n = 48)	• Not reported	• Overall survival • Progression-free survival	Serious
Yoshino (2022) Japan - five affiliated institutions	N = 41 Patients with synchronous metastatic renal cell carcinoma	Upfront cytoreductive nephrectomy then nivolumab plus ipilimumab initiation (n = 21)	No cytoreductive nephrectomy (n = 13) Nivolumab plus ipilimumab +	• Not reported	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
Study dates: September 2016 and July 2021	Key exclusion criteria: Patients whose duration of post-treatment follow-up was short (i.e. <1 month) or whose clinical data were missing		deferred cytoreductive nephrectomy (n = 7)			
You (2021) Republic of Korea Study dates: November 2006 to December 2009	N = 78 Patients diagnosed with metastatic renal clear cell carcinoma Key exclusion criteria: Non-clear cell type renal cell carcinoma, no evidence of residual disease due to complete nephrectomy and metastasectomy	Cytoreductive nephrectomy + targeted therapy (n = 45)	Targeted therapy alone (n = 33)	• Memorial Sloan-Kettering Cancer Centre prognostic factors	• Overall survival • Progression-free survival	Serious

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Clinical decision thresholds for minimally important differences (MIDs) were used to interpret the evidence. The line of no effect (in this case represented by 1.0) was used as a clinical decision threshold for the outcomes of overall survival, mortality, progression-free survival, cancer specific survival, duration of hospital stay, and complications grade ≥3 (Clavien Dindo). No data was identified for need for further systemic therapy, and quality of life.

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

- For outcomes without a defined MID or where the MID is set as the line of no effect, evidence statements are divided into 2 groups as follows:
    - We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
    - It is not possible from the evidence to differentiate between comparators if the 95% CI crosses the line of no effect.

Further details on GRADE assessment are described in appendix F.

Cytoreductive nephrectomy (CN) followed by systemic anti-cancer therapy (SACT) is summarised as "upfront CN". CN delivered after SACT is summarised as "deferred CN".

Upfront cytoreductive nephrectomy (CN) vs. deferred CN

Survival outcomes

Table 4: Survival outcomes comparing upfront cytoreductive nephrectomy and then systemic anti-cancer therapy versus systemic anti-cancer therapy followed by cytoreductive nephrectomy

Number of studies	Study design	Outcome	Histological type	Sample size	Effect estimate	Certainty	Interpretation of effect
2 (Bex 2018, Shen 2023)	Randomised controlled trial	Progression-free survival, ≤5 years	Clear cell	183	HR 1.35 (0.94 to 1.95)	Very low	Could not differentiate
1 (Gunenc 2024)	non-randomised study	Progression-free survival, ≤5 years	Mixed	51	HR 0.40 (0.12 to 1.39)	Very low	Could not differentiate
2 (Bex 2018, Shen 2023)	Randomised controlled trial	Overall survival, ≤5 years	Clear cell	183	HR 1.54 (1.02 to 2.32)	Low	Effect favours deferred cytoreductive nephrectomy
2 (Meagher 2024, Stroup 2013)	Non-randomised controlled trial	Cancer-specific survival, ≤5 years	Clear cell	217	HR 2.15 (1.43 to 3.25)	Very low	Effect favours deferred cytoreductive nephrectomy
8 (Bhindi 2018, Bhindi 2020, Ghatalia 2022, Gunenc 2024, Macleod 2018, Meagher 2024,Singla 2020, Stroup 2013)	Non-randomised controlled trial	Overall survival, ≤5 years	Mixed	17,731	HR 0.94 (0.70 to 1.28)	Very low	Could not differentiate

Number of studies	Study design	Outcome	Histological type	Sample size	Effect estimate	Certainty	Interpretation of effect
2 (Takemura 2024, Yoshino 2022*)	Non-randomised controlled trial	Mortality, ≤5 years	Mixed	395	RR 5.08 (1.03 to 25.03)	Very low	Effect favours deferred cytoreductive nephrectomy
1 (Hatakeyama 2021)	Non-randomised controlled trial	Overall survival, >5 years	Mixed	146	HR 1.64 (0.87 to 3.09)	Very low	Could not differentiate

* Converted from 'overall survival' reported as events
Reasons for downgrading can be found in the full GRADE tables in appendix F.

All other outcomes

Table 5: All other outcomes comparing upfront cytoreductive nephrectomy and then systemic anti-cancer therapy versus systemic anti-cancer therapy followed by cytoreductive nephrectomy

Number of studies	Study design	Outcome	Histological type	Sample size	Effect estimate	Certainty	Interpretation of effect
1 (Bex 2018)	Randomised controlled trial	Adverse events grade ≥3 (Clavien Dindo)	Clear cell	80	RR 0.45 (0.05 to 4.15)	Very low	Could not differentiate
1 (De Bruijn 2019)	Randomised controlled trial	Duration of hospital stay - Days	Clear cell	80	MD 1.00 (-1.35 to 3.35)	Very low	Could not differentiate
1 (Patel 2016)	Non-randomised controlled trial	Adverse events grade ≥3 (Clavien Dindo)	Clear cell	48	RR 0.06 (0.00 to 1.02)	Very low	Could not differentiate
1 (Patel 2016)	Non-randomised controlled trial	Duration of hospital stay - Days	Clear cell	48	MD -2.50 (-6.19 to 1.19)	Very low	Could not differentiate

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

Upfront cytoreductive nephrectomy (CN) vs. no CN (systemic anti-cancer therapy, SACT, alone)

Survival outcomes

Table 6: Survival outcomes comparing upfront cytoreductive nephrectomy and then systemic anti-cancer therapy versus systemic anti-cancer therapy alone

Number of studies	Study design	Outcome	Histological type	Sample size	Effect estimate	Certainty	Interpretation of effect
1 (Méjean 2018)	Randomised controlled trial	Progression-free survival, ≤5 years	Clear cell	399	HR 0.82 (0.67 to 1.00)	Very low	Could not differentiate
1 (Méjean 2021)	Randomised controlled trial	Overall survival, ≤5 years	Clear cell	450	HR 0.97 (0.79 to 1.19)	Very low	Could not differentiate
3 (Hara 2023, Xu 2019, You 2011)	Non-randomised controlled trial	Progression-free survival, ≤5 years	Clear cell	350	HR 0.73 (0.39 to 1.37)	Very low	Could not differentiate
1 (Stroup 2013)	Non-randomised controlled trial	Cancer specific survival, ≤5 years	Clear cell	35	HR 0.10 (0.02 to 0.42)	Very low	Effect favours upfront cytoreductive nephrectomy
11 (Bakouny 2023, Bhindi 2020, Chakiryan 2022, Choueiri 2011, Dragomir 2022, de Groot 2016, Ghatalia 2022, Hara 2023, Manley 2017, Xu 2019, You 2011)	Non-randomised controlled trial	Overall survival, ≤5 years	Mixed	20,957	HR 0.67 (0.54 to 0.82)	Very low	Effect favours upfront cytoreductive nephrectomy

Number of studies	Study design	Outcome	Histological type	Sample size	Effect estimate	Certainty	Interpretation of effect
2 (Takemura 2024, Yoshino 2022*)	Non-randomised controlled trial	Mortality, ≤5 years	Mixed	801	RR 0.56 (0.41 to 0.76)	Low	Effect favours upfront cytoreductive nephrectomy
2 (Hatakeyama 2021, Poprach 2020)	Non-randomised controlled trial	Overall survival, >5 years	Mixed	969	HR 0.57 (0.47 to 0.68)	Low	Effect favours upfront cytoreductive nephrectomy

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

All other outcomes

Table 7: All other outcomes comparing upfront cytoreductive nephrectomy and then systemic anti-cancer therapy versus systemic anti-cancer therapy alone

Number of studies	Study design	Outcome	Histological type	Sample size	Effect estimate	Certainty	Interpretation of effect
1 (Méjean 2018)	Randomised controlled trial	Adverse events grade ≥3	Mixed	399	RR 0.77 (0.59 to 0.99)	Very low	Effect favours upfront cytoreductive nephrectomy
1 (Hara 2023)	Non-randomised controlled trial	Adverse events grade ≥3 (Clavien Dindo)	Mixed	54	RR 1.75 (0.85 to 3.57)	Very low	Could not differentiate

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

See appendix F for full GRADE tables.

1.1.7 Economic evidence

Evidence review H contains two parts (H1 and H2). A single literature search was conducted to identify published economic evaluations of relevance to the review questions on the management of RCC in this guideline (see appendix B), which includes both H1 and H2 for the management of advanced RCC, as well as reviews for the management of localised RCC (evidence review A and evidence review B) and locally advanced RCC (evidence review C).

This search retrieved 326 studies and based on title and abstract screening four studies were identified as potentially relevant for any of the evidence reviews covered by the search. On review of the full text, two studies were included for evidence review B, and two studies were excluded. For details on study selection, see economic study selection flow chart in appendix G.

1.1.7.1 Included studies

No economic evidence was identified for the present review questions H1 and H2 on the non-pharmacological management of advanced RCC. Two economic studies were included in evidence review B on non-surgical interventions or active surveillance in adults with localised RCC (see evidence review B for details).

1.1.7.2 Excluded studies

Two studies were excluded at full text review (see appendix J for a list of studies and reasons for exclusion).

1.1.8 Economic model

No original economic modelling was conducted for this review.

1.1.9 Unit costs

Unit costs of interventions are listed in Table 8.

Table 8: Unit costs of interventions

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 the robotic nephrectomy unit cost.

Resource	Unit cost	Source
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
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
Metastasectomy	£4,160.46 - £6,774.33	NHS Cost Collection (2024). LB06J-M Kidney urinary tract or prostate neoplasms with interventions and DZ17P-R Respiratory neoplasms with single intervention

SABR: stereotactic ablative radiotherapy, CT: computed tomography

1.1.10 The committee's discussion and interpretation of the evidence

Evidence review H contains two parts (H1 and H2). The committee discussed both parts of the evidence review together, and there is a single discussion section to record this. See section 2.1.8 for the full discussion.

1.1.11 References – included studies

1.1.12.1 Effectiveness – randomised controlled trials

Bex A, Mulders P, Jewett M et al. (2019) Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. JAMA oncology 5(2): 164-170

De Bruijn R.E, Mulders P, Jewett M. A et al. (2019) Surgical Safety of Cytoreductive Nephrectomy Following Sunitinib: Results from the Multicentre, Randomised Controlled Trial of Immediate Versus Deferred Nephrectomy (SURTIME). European urology 76(4): 437-440

Mejean A, Ravaud A, Thezenas S et al. (2021) Sunitinib Alone or After Nephrectomy for Patients with Metastatic Renal Cell Carcinoma: Is There Still a Role for Cytoreductive Nephrectomy?. European urology 80(4): 417-424

Mejean A, Ravaud A, Thezenas S et al. (2018) Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. The New England journal of medicine 379(5): 417-427

Shen X-P, Xie M, Wang J-S et al. (2023) Efficacy of immunotherapy-based immediate cytoreductive nephrectomy vs. deferred cytoreductive nephrectomy in metastatic renal cell carcinoma. European review for medical and pharmacological sciences 27(12): 5684-5691

1.1.12.2 Effectiveness – non-randomised controlled trials

Bakouny Z, El Zarif T, Dudani S et al. (2023) Upfront Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma Treated with Immune Checkpoint Inhibitors or Targeted Therapy: An Observational Study from the International Metastatic Renal Cell Carcinoma Database Consortium. European urology 83(2): 145-151

Bhindi B, Habermann E.B., Mason R.J. et al. (2018) Comparative Survival following Initial Cytoreductive Nephrectomy versus Initial Targeted Therapy for Metastatic Renal Cell Carcinoma. Journal of Urology 200(3): 528-534

Bhindi B, Graham J, Wells JC et al. (2020) Deferred Cytoreductive Nephrectomy in Patients with Newly Diagnosed Metastatic Renal Cell Carcinoma. European urology 78(4): 615-623

Chakiryan N.H, Gore L.R, Reich R.R et al. (2022) Survival Outcomes Associated With Cytoreductive Nephrectomy in Patients With Metastatic Clear Cell Renal Cell Carcinoma. JAMA network open 5(5): e2212347

Choueiri T.K, Xie W, Kollmannsberger C et al. (2011) The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. The Journal of urology 185(1): 60-6

de Groot S, Redekop W.K, Sleijfer S et al. (2016) Survival in Patients With Primary Metastatic Renal Cell Carcinoma Treated With Sunitinib With or Without Previous Cytoreductive Nephrectomy: Results From a Population-based Registry. Urology 95: 121-7

Dragomir A, Nazha S, Tanguay S et al. (2022) Outcomes of Cytoreductive Nephrectomy for Patients with Metastatic Renal Cell Carcinoma: Real World Data from Canadian Centers. European Urology Focus 8(6): 1703-1710

Ghatalia P, Handorf E.A, Geynisman D M et al. (2022) The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma: A Real-World Multi-Institutional Analysis. The Journal of urology 208(1): 71-79

Gunenc D, Issa W, Gerald T, Zhou Q, Zhang S et al. Pathological Response and Outcomes in Patients With Metastatic Renal Cell Carcinoma (mRCC) Receiving Immunotherapy-Based Therapies and Undergoing Deferred Cytoreductive Nephrectomy (CN). Clin Genitourin Cancer 22(5): 102177.

Hara T, Furukawa J, Shiraishi Y et al. (2023) Impact of cytoreductive nephrectomy prior to combination therapy of ipilimumab plus nivolumab in metastatic renal cell carcinoma. International journal of urology : official journal of the Japanese Urological Association 30(9): 746-752

Hatakeyama S, Naito S, Numakura K et al. (2021) Impact of cytoreductive nephrectomy in patients with primary metastatic renal cell carcinoma receiving systemic tyrosine kinase inhibitor therapy: A multicenter retrospective study. International journal of urology : official journal of the Japanese Urological Association 28(4): 369-375

Macleod L.C, Odisho A.Y, Tykodi S.S et al. (2018) Comparative Effectiveness of Initial Surgery vs Initial Systemic Therapy for Metastatic Kidney Cancer in the Targeted Therapy Era: Analysis of a Population-based Cohort. Urology 113: 146-152

Manley B.J, Kim E.H, Vetter J.M et al. (2017) Validation of preoperative variables and stratification of patients to help predict benefit of cytoreductive nephrectomy in the targeted therapy ERA. International braz j urol : official journal of the Brazilian Society of Urology 43(3): 432-439

Meagher M, Minervini A, Mir M.C, Cerrato C, Rebez G et al. (2024) Does the Timing of Cytoreductive Nephrectomy Impact Outcomes? Analysis of REMARCC Registry Data for Patients Receiving Tyrosine Kinase Inhibitor Versus Immune Checkpoint Inhibitor Therapy. Eur Urol Open Sci 63(25): 71 – 80

Patel N, Woo J, Liss M.A et al. (2016) Does timing of targeted therapy for metastatic renal cell carcinoma impact treatment toxicity and surgical complications? A comparison of primary and adjuvant approaches. The Canadian journal of urology 23(2): 8227-33

Poprach A, Holanek M, Chloupkova R et al. (2020) Cytoreductive Nephrectomy and Overall Survival of Patients with Metastatic Renal Cell Carcinoma Treated with Targeted Therapy-Data from the National Renis Registry. Cancers 12(10)

Singla N, Hutchinson R.C, Ghandour R.A et al. (2020) Improved survival after cytoreductive nephrectomy for metastatic renal cell carcinoma in the contemporary immunotherapy era: An analysis of the National Cancer Database. Urologic oncology 38(6): 604e9-604e17

Stroup S.P, Raheem O.A, Palazzi K. L et al. (2013) Does timing of cytoreductive nephrectomy impact patient survival with metastatic renal cell carcinoma in the tyrosine kinase inhibitor era? A multi-institutional study. Urology 81(4): 805-11

Takemura K, Ernst M.S, Navani V et al. (2023) Characterization of Patients with Metastatic Renal Cell Carcinoma Undergoing Deferred, Upfront, or No Cytoreductive Nephrectomy in the Era of Combination Immunotherapy: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. European urology oncology

Xu W.-H, Wang J, Huo D.-Z et al. (2019) C-reactive protein levels and survival following cytoreductive nephrectomy in 118 patients with metastatic renal cell carcinoma treated with sunitinib: A retrospective study. Medical Science Monitor 25: 8984-8994

Yoshino M, Ishihara H, Nemoto Y et al. (2022) Therapeutic role of deferred cytoreductive nephrectomy in patients with metastatic renal cell carcinoma treated with nivolumab plus ipilimumab. Japanese journal of clinical oncology 52(10): 1208-1214

You D, Jeong I.G, Ahn J-H et al. (2011) The value of cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy. The Journal of urology 185(1): 54-9

1.1.12.3 Economic

No economic studies were included.

1.1.12.4 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/ [online; accessed 2 July 2025]

2 Management of advanced renal cell carcinoma using non-pharmacological interventions after systemic anti-cancer therapy

2.1 Review question

What is the clinical and cost-effectiveness of non-pharmacological interventions used after systemic anti-cancer therapy for adults with advanced renal cell carcinoma?

2.1.1 Introduction

There are number of treatment options available for advanced renal cell carcinoma. These usually include pharmacological (systemic anti-cancer therapy, SACT) and non-pharmacological interventions. It is important to understand the sequence of these treatment modalities for reducing disease burden and improving survival benefits in the most effective manner.

Therefore, this review aims to evaluate the clinical and cost-effectiveness of non-pharmacological interventions after initial treatment with SACT in managing advanced renal cell carcinoma. Review H1 assesses the clinical and cost-effectiveness of non-pharmacological interventions before SACT.

2.1.2 Summary of the protocol

Table 9: PICO inclusion criteria

Population	Adults (18 years or over) with advanced RCC* who have previously received systemic anti-cancer treatment (SACT). *defined as metastatic/ advanced RCC or locally advanced inoperable RCC (histologically confirmed or suspected on imaging). Advanced RCC diagnosis confirmed according to the clinical or pathological TNM classification Exclusion: • Adults with localised or locally advanced disease that is considered to be operable. • Adults with advanced disease who are having palliative care only.

Interventions	• Non-pharmacological procedures carried out after SACT to manage primary mass:
	  ○ Cytoreductive nephrectomy
	  ○ Stereotactic ablative radiotherapy (SABR)
	• Managing metastases:
	  ○ Surgical removal
	  ○ Thermal ablation:

	▪ Radiofrequency ablation ▪ Cryotherapy ▪ Microwave ablation ○ Radiotherapy: ▪ External beam radiotherapy (EBRT) ▪ Stereotactic ablative radiotherapy (SABR)
Comparator	When both arms have previously had SACT for advanced RCC: • No intervention (compared with non-pharma intervention) When neither arm has previously had SACT for advanced RCC: • SACT (compared with SACT then non-pharma intervention)
Outcomes	• Progression-free survival • Overall survival or if not reported: ○ Mortality • Cancer-specific survival or if not reported: ○ Cancer-specific mortality • Severe adverse events reported as: ○ observed in the intraoperative period ○ observed in postoperative period • Need for further systemic therapy • Number of hospital admissions • Duration of hospital stay • Quality of life
Study type	• Randomised controlled trials (RCTs) • Any controlled, non-randomised studies • Cohort studies (prospective and retrospective observational studies) • Systematic reviews of the above studies

For the full protocol see appendix A. Note: this PICO reflects the protocol deviations (see section 2.1.3.2 for details).

2.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, the text below and the methods document.

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

1. Mortality at timepoints of 90 days or less was not included in this review. This was considered to be within the postoperative period and therefore covered by the outcome of postoperative severe adverse events (PSAE). PSAE was required to be reported using the acceptable classifications - Clavien-Dindo classification or Common Terminology Criteria for Adverse Events (CTCAE) in order to be included.
2. Where more than 1 timepoint was reported we reported data at up to 5 years and 5 to 10 years. Where several time points were reported that could fit in the same category, the latest time point was used.

3. For outcomes where the line of no effect was defined as the minimal important difference (MID), a power calculation from a robust RCT (Mejean 2018, included in this review) was used to determine the minimum sample size needed for consideration for the second downgrade criteria for the imprecision domain in GRADE. One RCT was identified which compared upfront cytoreductive nephrectomy with sunitinib alone (Méjean 2018). This trial does not meet the inclusion criteria for this review, but is related. It was used as a source to inform the minimum sample size needed. For all outcomes sample size of less than 576 was used for downgrading.
4. Important confounders considered for assessing the quality of the included studies under this review were discussed and agreed with the committee. These confounders were:
    - Age
    - TNM classification
    - Primary RCC type e.g. clear cell, papillary and chromophobe
    - Tumour grade
    - Renal function at baseline
    - Performance status of participants at baseline
    - Location and number of metastases
    - Type of SACT previously received.

2.1.3.1 Search methods

The searches for the effectiveness evidence were run on 18/01/2024 and re-run on 14/02/2025. The following databases were searched: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), Epistemonikos (Epistemonikos) and MEDLINE ALL (Ovid). Limits were applied to remove animal studies, conference abstracts, editorials, letters, news items and commentaries, as well as papers not published in the English language. Filters were used to limit to OECD countries, systematic reviews, randomised controlled trials and observational studies.

The searches for the cost effectiveness evidence were run between 05/01/2024 and 07/01/2024 and re-run on 06/05/2025. The following databases were searched: EconLit (Ovid), Embase (Ovid), HTA (CRD), International HTA database (INAHTA), MEDLINE ALL (Ovid) and NHS Economic Evaluations Database (CRD). Limits were applied to remove animal studies, conference abstracts, editorials, letters, news items and commentaries, as well as papers not published in the English language. Filters were used to limit to OECD countries and cost utility 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.

2.1.3.2 Protocol deviations

1. Severe adverse event classifications were further specified:

- The Intraoperative Adverse Incident Classification (EAUiaiC) and Clavien-Dindo Classification, both of which were already specified in the protocol, were used for thermal ablation and surgery interventions only.
- The Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 was added to the protocol to be used for SABR and EBRT interventions only, or for comparisons where one arm was SACT only. This addition aligns this protocol with others in this guideline (reviews A, B and C) and reflects the fact that Clavien-Dindo is usually used for surgery.

2. The quality of life outcomes were extracted when measured using EORTC Core Quality of Life Questionnaire and EuroQol-5 dimensions (EQ-5D). Later in the process it was agreed to include two additional scales assessing the quality of life outcomes. These two additional scales were:
    - Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index (FKSI: both the FKSI-15 and the FKSI-DRS)
    - Renal Cell Carcinoma Symptom Index (RCC-SI)
3. Initially it was decided that the population to be included in this review will be people who have previously received systemic anti-cancer treatment (SACT). This decision had the possibility of potentially missing out the population who only received SACT during the study. A protocol deviation was made to include people who had not previously received SACT for advanced RCC but who received SACT in the course of the study. This meant that there were two possible comparisons for this review:

- In people who have all previously had SACT for advanced RCC: Non-pharma intervention vs no intervention.
- In people who have never had SACT for advanced RCC: SACT then non-pharma intervention vs SACT alone.

2.1.4 Effectiveness evidence

2.1.4.1 Included studies

A single systematic search was carried out to identify potentially relevant studies for the current review (review H2) and reviews A, B, C and H1 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: non-pharmacological management of advanced RCC). This search found 19,882 references (see appendix B for the literature search strategy).

These 19,882 references were screened at title and abstract level against the review protocols, with 19,208 excluded at this level. 176 articles were assessed at full text for review H (H1 and H2 combined) (the remainder of those not excluded at title and abstract were assessed at full text stage for review A, B or C). 10% of references were screened separately by two reviewers with 99.9% agreement. Discrepancies were resolved by discussion.

The full texts of 176 references were ordered for closer inspection. A total of 7 articles, all retrospective cohort studies, met the criteria specified in the review protocol for review H2 (appendix A). All studies compared deferred cytoreductive nephrectomy (cytoreductive nephrectomy after systemic anti-cancer therapy) with systemic anti-cancer therapy alone. Six

out of 7 included cohort studies reported similar outcomes (overall survival) and one study reported cancer specific survival data.

For a summary of the 7 articles included in this review see Table 10.

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

2.1.4.2 Excluded studies

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

2.1.5 Summary of studies included in the effectiveness evidence

Table 10: Summary of characteristics of the included non-randomised studies

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
Bhindi (2018) United States – utilises NCDB database Study dates: 2006 - 2013	N= NR People with metastatic kidney cancer. Key exclusion criteria: any other carcinoma, missing data, not receiving treatment within 3 months of diagnosis.	Deferred cytoreductive nephrectomy (n=7520) Type of SACT – not reported	SACT alone (n=NR) Type of SACT – not reported	Age, sex, race, Charlson co-morbidity index, income, educational status, country, facility location, facility type, primary tumour histology, TNM classification	• Overall survival	Serious
Bhindi (2020) IMDC database (33 centres globally) Study dates: 2006 to 2018	N=736 People receiving sunitinib as first line systemic anti-cancer therapy. Key exclusion criteria: unknown timings of surgery, missing data, SACT after 12 months of diagnosis.	Deferred cytoreductive nephrectomy (n=85) Type of SACT – first-line therapy with sunitinib	SACT alone (n=651) Type of SACT – sunitinib	Age, sex, year of diagnosis, IMDC risk, clear cell histology, number of metastatic sites, location of metastases	• Overall survival	Serious
Chakiryan (2022)	N=8328	Deferred cytoreductive nephrectomy (n=612)	SACT alone (n=7716)	Age, sex, race, Charlson-Deyo score, year of	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
United States – utilises NCDB database Study dates: 2006 to 2016	People with metastatic renal cancer with complete data.	Type of SACT – targeted therapy as first-line treatment	Type of SACT – targeted therapy as first-line treatment	diagnosis, clinical staging, cytoreductive nephrectomy status.		
Day (2016) Australia Study dates: 2006 to 2012	N=76 People with metastatic renal cancer and complete data. Key exclusion criteria: received SACT before January 2006.	Deferred cytoreductive nephrectomy (n=42) Type of SACT – first-line treatment with sunitinib (n= 33), Pazopanib (n= 4), Bevacizumab (n= 2), Interferon (n= 2), temsirolimus (n= 1)	SACT alone (n=34) Type of SACT – first-line treatment with sunitinib (n= 34), everolimus (n= 4)	Cytoreductive nephrectomy (CN), MSKCC risk classification, neutrophil-to-lymphocyte ratio, histology and systemic treatment	• Overall survival	Serious
Dragomir (2022) Canada – utilises Canadian Kidney Cancer information system Study dates: 2011 to 2020	N=325 People with histologically diagnosed renal cell carcinoma. Key exclusion criteria: People with indolent metastatic disease	Deferred cytoreductive nephrectomy (n=73) Type of SACT – sunitinib (n=52), pazopanib (n=8), ipilimumab / nivolumab (n=3), nivolumab / everolimus / pembrolizumab / temsirolimus / atezolizumab / axitinib / lenvatinib (n= 10)	SACT alone (n=252) Type of SACT – sunitinib (n=121), pazopanib (n=52), ipilimumab / nivolumab (n=57), nivolumab / everolimus / pembrolizumab / temsirolimus / atezolizumab / axitinib / lenvatinib (n= 22)	Age, sex, sites and number of organs for metastasis, cell histology, IMDC risk and Charlson comorbidity index	• Overall survival	Serious

Study details	Population	Intervention	Comparator	Confounders the study adjusted for	Outcomes	Risk of bias
Fransen (2023) Netherlands and England Study dates: 2019 to 2022	N=26 People with histologically diagnosed renal cell carcinoma. Key exclusion criteria: NR	Deferred cytoreductive nephrectomy (n=19) Type of SACT – first-line therapy with ipilimumab-nivolumab	SACT alone (n=7) Type of SACT – first-line therapy with ipilimumab-nivolumab	Not stated	• Cancer-specific mortality	Serious
Hatakeyama (2021) Japan Study dates: 2008 to 2019	N=171 People with primary metastatic renal cell carcinoma. Key exclusion criteria: missing data, fist-line treatment other than kinase inhibitors, follow-up less than 3 months.	Deferred cytoreductive nephrectomy (n=39) Type of SACT – first-line therapy with TKI – sunitinib (n= 17), sorafenib (n=2), axitnib (n= 19), Pazopanib (n=1)	SACT alone (n=132) Type of SACT – first-line therapy with TKI – sunitinib (n= 65), sorafenib (n=16), axitnib (n= 47), Pazopanib (n=4)	Age, sex, performance status, IMDC risk factors, clinical staging, number of metastatic organs	• Overall survival	Moderate

SACT: systemic anti-cancer therapy; NR: not reported. Risk of bias: risk of bias of reported outcomes

See appendix D for full evidence tables

2.1.6 Summary of the effectiveness evidence

Clinical decision thresholds for minimally important differences (MIDs) were used to interpret the evidence. The line of no effect (in this case represented by 1.0) was used as a clinical decision threshold for the outcomes of overall survival and cancer specific survival. No data was identified for progression-free survival, intraoperative or postoperative severe adverse events, need for further systemic therapy, number of hospital admissions, duration of hospital stay and quality of life.

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

- For outcomes without a defined MID or where the MID is set as the line of no effect, evidence statements are divided into 2 groups as follows:
    - We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
    - The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

Cytoreductive nephrectomy (CN) delivered after systemic anti-cancer therapy (SACT) is summarised as "deferred CN". SACT alone refers to participants who did not receive CN either before or after SACT.

Table 11: Deferred cytoreductive nephrectomy (CN) vs systemic anti-cancer therapy (SACT) alone

Number of studies	Outcome	Sample size	Effect estimate	Certainty	Interpretation of effect
6 (Bhindi 2018, Bhindi 2020, Chakiryan 2022, Day 2016, Dragomir 2022, Hatakeyama 2021)	Overall survival ≤5 years	17,080[a]	HR 0.43 (0.37 to 0.51)	Low	Effect favours deferred CN
1 (Fransen 2023)	Cancer-specific mortality ≤5 years	26	RR 0.83 (0.61 to 1.11)	Very low	Could not differentiate

a. Bhindi 2018 does not report the number of participants for SACT alone arm.

Included studies only reported overall survival and cancer-specific mortality outcomes.

See appendix F for full GRADE tables and further details on GRADE assessment.

2.1.7 Economic evidence

Evidence review H contains two parts (H1 and H2). One review was conducted for all questions relating to the management options for RCC, which includes both H1 and H2 for the management of advanced RCC, as well as reviews for the management of localised RCC (evidence review C) and locally advanced RCC (evidence review A and evidence review B).

The review is described in section 1.1.7 Economic evidence. Unit costs relevant for this review are described in section 1.1.9 Unit costs.

2.1.8 The committee's discussion and interpretation of the evidence

Evidence review H contains two parts (H1 and H2). The committee discussed both parts of the evidence review together, and there is therefore a single discussion section to record this.

Note about the terminology used in this review: Cytoreductive nephrectomy (CN) followed by systemic anti-cancer therapy (SACT) is summarised as "upfront CN". CN delivered after SACT is summarised as "deferred CN". The committee noted whilst these terms have been used throughout the review and discussion sections, they preferred to use "CN before SACT" and "CN after SACT has been started" for the recommendations as they are more easily understood.

2.1.8.1. The outcomes that matter most

The committee agreed that survival outcomes (overall survival, progression free survival and cancer specific survival) and quality of life outcomes were of most importance as they are the best indicators to evaluate the effectiveness of each treatment pathway and they indicate the impact of surgical and non-surgical interventions on the lives of people diagnosed with metastatic renal cell carcinoma (mRCC), respectively. However, no evidence was identified for quality of life outcomes.

Of importance, but less so than the outcomes above, were severe adverse events, need for systemic therapy, number of hospital admissions and duration of hospital stay. These outcomes impact people's quality of life and health status in the short and long term and may also play an important role in deciding which treatment pathway is best for individuals as well as being indicative of the relative resource impact of the treatment. However, no evidence was identified for the outcomes of need for further systemic therapy and number of hospital admissions.

2.1.8.2 The certainty of the evidence

This review was conducted in two parts. The first part of the review explored the impact of non-pharmacological interventions before systemic anti-cancer therapy (SACT) (H1) whilst the second part looked at the effectiveness of non-pharmacological intervention after SACT (H2). The majority of the evidence for both reviews came from non-randomised studies, however, some randomised trials were included for H1.

Overall, the evidence from both parts of the review was graded as low or very low certainty, with the majority being very low certainty when assessed using GRADE. Much of the evidence was downgraded for the risk of bias domain due to more than 50% of the weight of the meta-analysis coming from outcomes at serious or moderate risk of bias:

- The outcomes from RCTs were rated as at moderate risk of bias due to a lack of clarity about the randomisation process, and some deviation from the intended interventions. The committee interpreted the results from two of the included RCTs – Bex et al. (2019) (SURTIME trial) and Méjean et al. (2021) (CARMENA trial) with caution. They noted that the SURTIME trial reported overall survival as a secondary outcome and the CARMENA trail failed to accrue sufficient participants, resulting in low power to detect a treatment effect.

- The evidence from non-randomised studies was downgraded mostly due to the bias arising from insufficient adjustment of confounding variables in the analysis, limited reporting or missing data. The committee agreed it was likely that participants were selected based on treatment suitability. This would mean that arms including a non-pharmacological intervention would be likely to include people with a better performance status or lower metastatic burden at baseline. They agreed that even where all confounders specified in the protocol were adjusted for, there would always be a chance of residual confounders. This would be likely to bias results towards arms containing a non-pharmacological intervention (when compared with SACT alone), or towards upfront non-pharmacological intervention (when compared with deferred non-pharmacological intervention). Therefore, the committee was very cautious about putting too much weight on the evidence from the non-randomised studies.

The certainty of the evidence from both RCTs and non-RCTs was also downgraded due to imprecision (where the effect estimate crossed the line of no effect, and the sample size was smaller than 576) and inconsistency (where the I^2 value was high, or the outcome was contributed to by a single study).

This review looked at interventions to treat the primary renal mass and the metastases. There was only evidence of cytoreductive nephrectomy (CN) as an intervention to treat the primary renal mass before or after SACT. No evidence was identified for other interventions specified in the protocol (for treating the primary mass: stereotactic ablative radiotherapy [SABR]; for treating the metastases: metastasectomy, thermal ablation, external beam radiotherapy [EBRT] or SABR). The committee were aware of ongoing trials that will be of relevance for this review in the future. See the section on 'other factors the committee took into account' for more details and for information about 2 of the research recommendations they drafted.

The population of interest for these reviews was people with advanced renal cell carcinoma (RCC) – that is, RCC which is metastatic or locally advanced and inoperable. Because the only interventions identified in the studies were surgical, there was no evidence to support specific management recommendations for people with locally advanced inoperable disease. The committee noted this gap in the evidence base and made a research recommendation for SABR in this population. As factors that would make the disease inoperable, such as proximity to or invasion of a critical organ such as the bowel, would also prevent SABR being delivered in this group, the research recommendation specifies SABR after SACT has been started. SACT may cause changes to the primary mass which make SABR a suitable treatment option. The committee noted that people with locally advanced inoperable RCC

are covered by recommendations about SACT also included in this guideline. (The Technology Appraisals (TAs) in the SACT section of the guideline apply to people with advanced RCC – that is, people with metastatic, or locally advanced and inoperable, RCC unless otherwise specified.)

The committee noted that there were other gaps in the evidence base:

- No randomised trials for SACT then CN compared with SACT alone were identified.
- No evidence was identified for the following outcomes: need for systemic therapy; number of hospital admissions; duration of hospital stay; and quality-of-life.

The committee highlighted that the therapeutic landscape for advanced (metastatic and locally advanced inoperable) RCC treatment has changed in recent years. There has been a shift away from tyrosine kinase inhibitors (TKIs), also known as the TKI era, and towards immunotherapies and combination therapy regimes. Sunitinib (a TKI) was the most common type of SACT used across the studies, while other studies failed to provide sufficient information on the type of SACT used. Therefore, the included evidence does not evaluate the role of non-pharmacological interventions in the setting of combination therapy which is currently practiced. The committee could not judge what impact the type of SACT had on the results, or how the results would differ if the studies had been conducted using combination therapy. They accepted this as a limitation of the evidence.

It was not possible to carry out most of the planned subgroup analyses due to too few studies in the meta-analysis or insufficient detail in the level of reporting to categorise participants. However, there were no subgroup differences when subgroup analysis based on histological subtype of renal cell carcinoma was carried out for overall survival ≤5 years for either the comparison of upfront CN compared with deferred CN (Figure 3), or upfront CN compared with SACT alone (Figure 14).

2.1.8.3 Benefits and harms

Referring people with advanced RCC

The committee highlighted that in current practice the decision about whether to use non-pharmacological interventions in addition to pharmacological treatment is a complex one that relies on assessment of the person's individual clinical characteristics (such as number and location of metastases, general health and comorbidities) as well as the their risk of progression, the risks and benefits of potential treatments, and the timing of any non-pharmacological interventions. They agreed that people with metastatic renal cell carcinoma should be referred to a uro–oncology multi-disciplinary team (MDT) with relevant expertise in managing kidney cancer surgery to facilitate this decision-making process. They also recognised that depending on the location of metastases (for example, in the brain, spine or lung), other treatments may be suitable to manage the metastases and that additional expertise from MDTs that specialise in those areas may be required. The committee made recommendations to reflect these points.

The committee were aware of other NICE guidelines that could be relevant for people with RCC who have metastases and they included cross references to the following: the section on recognising spinal metastases or MSCC in NICE's guideline on spinal metastases and metastatic spinal cord compression and the section on investigation of suspected brain metastases in NICE's guideline on brain tumours (primary) and brain metastases in over 16s.

Non-pharmacological treatments

The committee noted that the aim of SACT is to treat the metastases, as opposed to localised treatment which targets a specific lesion or small group of lesions. The committee noted that the evidence comparing upfront with deferred CN was low to very low certainty and therefore they could not draw any firm conclusions from it. However, the RCT evidence showed a statistically significant improvement in overall survival with deferred CN when compared to upfront CN (low certainty). The committee noted that this was consistent with current clinical practice of preferring deferred CN over upfront CN in most cases. They noted that lack of an observed effect in most of the non-randomised data could be due to bias towards the upfront CN arms (see "the certainty of the evidence" section).

The committee agreed that in their experience, people with oligometastatic cancer (cancer that has metastasised to a maximum of 3 sites, with a total of 5 or fewer metastatic lesions), who do not have symptoms are less likely to need SACT immediately. In these cases, regular imaging using CT could be used to monitor disease progression and to determine when SACT is needed. Although evidence for surveillance was not considered as part of this review, the committee highlighted the importance of monitoring people with oligometastatic cancer who do not have symptoms until they needed treatment and agreed that not including a recommendation on this would leave a clear gap in the guidance that could cause confusion. They therefore used their expertise and experience to make a recommendation to reflect this scenario. In addition, the committee highlighted that some people may not want to receive SACT immediately, due to the impact of side effects on their family life and ability to work.

The committee agreed that for people with widespread metastases (which is cancer that does not meet the definition of oligometastatic cancer as it has spread to more sites or there are more lesions overall), immediate SACT would usually be indicated to target the spread of the cancer. Initial treatment with SACT (before any non-pharmacological interventions) could potentially also reduce the size of the renal mass at the primary site. Reduced mass burden at metastatic and primary sites could also make people with metastatic RCC more likely to be eligible for a non-pharmacological intervention after SACT. Therefore, the committee agreed that offering any potential non-pharmacological interventions after, not before, treatment with SACT has been started was the best course of action for most people with widespread metastases. The committee acknowledged that there are exceptions where it may be appropriate to offer a non-pharmacological intervention before SACT. They agreed that treatment for symptoms related to metastases may be urgently needed, for example for metastatic spinal cord compression. See also below under treating the primary mass for further detail about this.

Treating the primary renal lesion

The committee noted that although some low and very low certainty evidence showed improved outcomes for upfront nephrectomy compared with SACT alone, whether surgery at this stage is appropriate would depend on the person's individual clinical characteristics, including the mass burden, site of the mass, extent of metastasis and overall health of a person, as well as clinical judgement of risks and benefits. They agreed that upfront CN would not be suitable for most people.

The committee discussed 2 scenarios where it might be appropriate to delay SACT in favour of surgery. In the first scenario, if SACT is not needed immediately and if surgery is suitable then CN could be used for oncological control (i.e. to reduce disease burden, prevent the

cancer from growing or causing symptoms). The committee was of the opinion that this could apply to people with a good performance status and low metastatic burden (for example, oligometastatic disease) where upfront removal of the primary mass could potentially improve survival outcomes (Figure 2).

In the second scenario, the committee discussed situations where people with metastatic RCC have severe symptoms related to their primary mass such as pain, bleeding and obstructive uropathy. In the committee's experience, surgically removing the primary mass can help alleviate these symptoms. The committee acknowledged that this review did not focus on using non-pharmacological interventions to relieve cancer symptoms, but it did include quality of life outcomes. Although no evidence was found relating to effects on quality of life, the committee used their clinical expertise to recommend that in cases where the person with metastatic RCC has symptoms that could be controlled by surgery, CN could be considered before or after SACT has been started for this purpose.

The committee agreed that in current practice CN is more likely to be performed when there has been at least a durable partial response to SACT in the metastatic sites and most of the disease that is left after SACT is in the primary site and used their expertise and experience to make a consider recommendation to reflect this. They also included in the recommendation that surgery would have to be suitable based on the clinical characteristics of the person and their renal lesion. They noted that deferred CN allows an assessment of how metastatic disease responds to initial systemic treatment. Where people have a good initial response to SACT, the primary mass may shrink, potentially making the surgery safer and easier, and leading to fewer surgical complications. The committee agreed that any SACT-induced reduction or control of metastases could lead to a reduced overall disease burden and better survival outcomes.

The committee discussed the definition of a durable partial response and advised that this referred to a decrease in renal lesion size of at least 30% of the sum of diameters of target measurable lesions compared with pre-treatment, that is observed at least 6 months after the start of treatment with systemic anticancer therapy and after at least 1 follow-up imaging scan.) They noted that this is consistent with the definition in the RECIST guidelines (RECIST 1.1 – RECIST).

The committee also highlighted the importance of taking into account people's wishes when offering non-pharmacological interventions i.e. if they want to have their primary mass removed. They noted that having cancer present in the body can be psychologically difficult for some people, and they may want to have CN to remove it, even if it is not clinically indicated. However, the committee agreed that there would be situations where this would not be possible, for example, if the individual is not able to have surgery based on their individual clinical characteristics. In other cases, CN to remove the primary mass may not be advisable before SACT is initiated, for example, if the person has fast growing metastases. In this scenario CN could be considered after SACT has been started if the person wants to have the primary tumour removed, surgery is suitable based on the individual's clinical characteristics, the person has had at least a durable partial response to SACT in the metastatic sites and most of the disease that is left after SACT is in the primary site. The committee recommended that when CN is not considered suitable for the person, this should be clearly explained to them because not removing the primary tumour may be difficult for some people to cope with, and understanding the reasons for this may help them come to terms with the situation.

Treating metastases

The committee acknowledged that there was no evidence identified for treatment of metastases using thermal ablation, SABR, external beam radiotherapy (EBRT) or metastasectomy. The committee noted that the decision to offer SABR, EBRT or thermal ablation for metastases varies on a case by case basis and depends on metastatic site, number of metastases and response to SACT (where SACT has already been received).

The committee discussed the use of EBRT to treat metastases. They were aware that SABR, a type of EBRT, is currently commissioned as a treatment option for people with a controlled primary cancer with up to three extracranial metachronous oligometastases which manifest after a disease-free interval of at least 6 months from primary treatment as outlined in the SABR commission policy. They agreed that SABR might give good local control of the disease and noted that it is usually used in controlling metastases where surgical resection is not an option or metastases are in areas that are difficult to treat surgically. SABR may be particularly effective for oligometastatic disease and can be used in the brain, liver, bones or other distant metastases. The committee also noted that thermal ablation may offer good control of metastases in brain, bone or liver.

In the committee's experience, metastasectomy can be an effective treatment option for localised metastatic deposits where no new lesions have occurred in the past 6 months and complete excision is achievable. The committee characterised this as 'no visible evidence of disease' and noted that this may be achieved in conjunction with CN. Taking these factors into account, the committee used their experience and expertise to make a consensus recommendation to consider the use of EBRT including SABR, thermal ablation or metastasectomy to treat metastases. They also made a separate recommendation to detail the specifics about when to consider metastasectomy reflecting the information above.

The committee were aware that NICE guidelines to treat spinal and brain metastases already exist and should be referred to for management of these metastases (for example, the sections on radiotherapy and invasive interventions in the NICE guideline on Spinal metastases and metastatic spinal cord compression, and the section on management of confirmed brain metastases in the NICE guideline Brain tumours (primary) and brain metastases in over 16s). In addition, as part of this review they had already made a recommendation about referral to MDTs that specialise in the area where the metastases are located where additional input or skills are needed to manage treatment of these patients (see above under the heading 'referring people with advanced RCC').

2.1.8.4 Cost effectiveness and resource use

No published economic evidence was identified and original economic modelling was not conducted for this evidence review. The committee were presented with unit costs of the relevant interventions and used their expertise to discuss potential resource use implications and changes to current clinical practice.

The committee recommended that cases of previously untreated metastatic RCC should be referred to specialist MDTs with the relevant expertise and indicated that in practice this is usually done but can be inconsistent in some areas. The recommendations made are expected to encourage standardisation of practice.

The committee recommended that treatment with SACT should be considered first for most people with metastatic RCC as this may be necessary to gain some control over the spread

of cancer and can potentially eradicate low burden RCC or shrink mass sizes. This type of control could improve outcomes for the patient and potentially reduce the risk of disease progression which in turn is beneficial from a cost-effectiveness perspective as progressed disease tends to have costly management and poor quality of life outcomes.

For non-pharmacological interventions in people with advanced RCC, the committee discussed all interventions currently used in practice and noted that practice is varied and is highly dependent on the individual case. The committee made 'consider' recommendations and stated the specific factors that should be thought about for each intervention, which should limit the use of interventions to those cases where it is most effective and therefore more likely to be cost-effective, while still ensuring individuals have the choice of options. It is not expected that these recommendations will substantially affect resource use given practice is already individualised according to the person's needs and preferences, and these recommendations should provide some standardisation of care across services.

2.1.8.5 Other factors the committee took into account

The committee highlighted that shared decision making is crucial in decisions about managing metastatic RCC. They stressed the importance of involving individuals in their own care to make a shared decision in choosing treatment options that align with people's values, goals and preferences. This collaborative approach empowers people with RCC, improves their satisfaction, and enhances clinical outcomes. It allows people to play an active role in their care, ensuring they are informed about their prognosis and the benefits and risks of available treatment options. By understanding these options, people with metastatic RCC are better equipped to make decisions that reflect their personal health goals and lifestyles. Shared decision making also helps clinicians to understand and tailor treatment options to the individual's priorities, such as avoiding side effects or opting for more aggressive therapies. The committee noted that each person will place a different weight on the benefits and harms of the available treatments to reach a decision. The committee was aware of the recommendations in NICE's shared decision-making process guideline that support the goals discussed above.

The committee was aware of and contributed to the Equality and Health Inequalities Impact Assessment (EHIA) for this guideline. They noted that health inequalities impact on the prevalence and incidence of kidney cancer, and also on people's access to and choice of treatment for RCC. In particular, they noted that for some people, the costs of attending treatment – especially where multiple or specialist treatments are required or where the treatment is not provided locally – could be prohibitive. This may be especially relevant for non-pharmacological interventions for metastatic RCC, which are usually offered at high-volume specialist centres. This problem may also be exacerbated if the person has less secure employment. The committee noted that this barrier to treatment also affects a wider population of people especially carers who accompany the people receiving the treatment.

The committee agreed that, although not specific to kidney cancer, referring to NICE's guidance on denosumab was important in the treating metastases section of the guideline to ensure clinicians' awareness of this treatment. Denosumab is recommended as an option for the prevention of skeletal-related events in adults with bone metastases from solid tumours other than prostate cancer.

The committee acknowledged the large gaps in the current evidence (see above under the certainty of the evidence for more details), including no evidence for non-pharmacological

interventions other than CN and no RCT evidence for deferred CN compared to SACT alone. They noted that there was also no evidence around the use of SABR to treat the primary mass. However, the committee were aware of ongoing randomised trials in these areas. Some of these trials evaluate the survival benefits of deferred CN compared with a no surgery group while others explore the role of SABR for treating primary mass:

- NORDIC-SUN and PROBE trial – both trials aim to evaluate the effectiveness and overall survival benefits of CN after SACT has been started when compared with no surgery group in treating primary metastatic RCC. Both arms will receive immunotherapy-based treatment. One of the main objectives of the trials is to demonstrate the need to personalise the most effective treatment pathway to avoid unnecessary overtreatment.
- CYTOSHRINK and SAMURAI trials – these trials aim to evaluate the effectiveness of adding SABR to standard combination therapy compared with SACT alone for treating metastatic primary RCC. Survival benefits are one of the primary outcomes of these trials.

Taking the gaps in the evidence base and the ongoing trails into account, the committee drafted the 3 research recommendations. The first research recommendation was aimed at providing information about whether metastasectomy was beneficial before systemic anticancer therapy (SACT) or after SACT has been started in people with metastatic RCC who have had their kidney and primary mass removed. The second research recommendation was aimed at determining the effectiveness of thermal ablation for treating metastases after SACT has been started in people with metastatic RCC. SABR was not included in this research recommendation due to the committee being aware of ongoing trials. The third research recommendation was aimed at determining the effectiveness of SABR to treat the primary mass after SACT has been started in people with locally advanced inoperable RCC.

2.1.9 Recommendations supported by this evidence review

Evidence review H contains two parts (H1 and H2). Evidence review H supports recommendations 1.12.1 to 1.12.2, and 1.14.1 to 1.14.8 and the research recommendations on (1) metastasectomy for metastatic RCC, (2) thermal ablation after SACT has been started for metastatic RCC and (3) SABR for treating the primary mass after SACT has been started in people with locally advanced inoperable renal cell carcinoma.

2.1.10 References – included studies

2.1.10.1 Effectiveness

Bhindi B, Habermann E.B., Mason R.J. et al. (2018) Comparative Survival following Initial Cytoreductive Nephrectomy versus Initial Targeted Therapy for Metastatic Renal Cell Carcinoma. Journal of Urology 200(3): 528-534

Bhindi B, Graham J, Wells J.C. et al. (2020) Deferred Cytoreductive Nephrectomy in Patients with Newly Diagnosed Metastatic Renal Cell Carcinoma. European urology 78(4): 615-623

Chakiryan N.H, Gore L.R., Reich R.R. et al. (2022) Survival Outcomes Associated With Cytoreductive Nephrectomy in Patients With Metastatic Clear Cell Renal Cell Carcinoma. JAMA network open 5(5): e2212347

Day D, Kanjanapan Y, Kwan E et al. (2016) Benefit from cytoreductive nephrectomy and the prognostic role of neutrophil-to-lymphocyte ratio in patients with metastatic renal cell carcinoma. Internal medicine journal 46(11): 1291-1297

Dragomir A, Nazha S, Tanguay S. et al. (2022) Outcomes of Cytoreductive Nephrectomy for Patients with Metastatic Renal Cell Carcinoma: Real World Data from Canadian Centers. European Urology Focus 8(6): 1703-1710

Fransen van de Putte. E.E, van den Brink L, Mansour M A et al. (2023) Indications and Outcomes for Deferred Cytoreductive Nephrectomy Following Immune Checkpoint Inhibitor Combination Therapy: Can Systemic Therapy be Withdrawn in Patients with No Evidence of Disease?. European urology open science 55: 15-22

Hatakeyama S, Naito S, Numakura K et al. (2021) Impact of cytoreductive nephrectomy in patients with primary metastatic renal cell carcinoma receiving systemic tyrosine kinase inhibitor therapy: A multicenter retrospective study. International journal of urology : official journal of the Japanese Urological Association 28(4): 369-375

2.1.10.2 Economic

No economic evidence was included.

2.1.11 References – other references

Mejean A, Ravaud A, Thezenas S et al. (2018) Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. The New England journal of medicine 379(5): 417-427

NHS England. National Cost Collection for the NHS 2023/24. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/. [online, accessed: 2 July 2025].

Appendices

Appendix A – Review protocols

Effectiveness review protocol H1

ID	Field	Content
1.	Review title	Clinical and cost-effectiveness analysis of non-pharmacological interventions, used before systemic anti-cancer therapy for adults with advanced renal cell carcinoma.
2.	Review question	What is the clinical and cost-effectiveness of non-pharmacological interventions used before systemic anti-cancer therapy for adults with advanced renal cell carcinoma?
3.	Objective	To evaluate the clinical and cost effectiveness of non-surgical interventions used before previous systemic anti-cancer treatments (SACT) for adults with advanced renal cell carcinoma (RCC). The aim of this review is to identify where there may be clinical benefit in carrying out a surgical or non-surgical procedure after SACT.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • INAHTA For the economics review the following databases will be searched: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA Searches will be restricted by: • Date limitations: None • English language • Human studies • Abstracts, conference presentations and theses will be excluded

		The full search strategies will be published in the final review.
5.	Condition or domain being studied	Advanced renal cell carcinoma
6.	Population	Adults (18 years or over) with advanced RCC* who have previously received cytoreductive nephrectomy (CN). *defined as metastatic/ advanced RCC or locally advanced inoperable RCC (histologically confirmed or suspected on imaging). Advanced RCC diagnosis confirmed according to the clinical or pathological TNM classification Exclusion: • Adults who have not received SACT. • Adults with localised or locally advanced disease that is considered to be operable. • Adults with advanced disease who are having palliative care only.

7.	Intervention	**Non-pharmacological procedures carried out before SACT to:**
		Manage primary mass:
		1. Surgical interventions (where metastatic RCC is considered operable)
		  • Cytoreductive nephrectomy in people without prior nephrectomy with or without surgical removal of lymph nodes (lymphadenectomy).
		2. Non-surgical interventions
		  • Stereotactic ablative radiotherapy (SABR)
		
		Manage metastases:
		3. Surgical interventions
		  • Surgical removal of metastases also known as metastasectomy (distinguish between complete and incomplete metastasectomy)
		
		4. Non-surgical interventions
		  • Thermal ablation including:
		  ▪ Radiofrequency ablation
		  ▪ Cryotherapy
		  ▪ Microwave ablation
		  • Radiotherapy:
		  ▪ External beam radiotherapy (EBRT)
		  ▪ Stereotactic ablative radiotherapy (SABR)

8.	Comparator	No non-pharmacological intervention after second or further-line SACT and SACT alone.
9.	Types of study to be included	• Systematic reviews of RCTs and RCTs are preferred where available for a comparison.

		• Where RCTs are not available for a comparison, systematic reviews of prospective and retrospective cohort studies and prospective and retrospective cohort studies will be considered. • Where good quality systematic reviews are identified, these may be used completely or as a source of references, depending on applicability. Alternatively, they may be updated by the addition of studies published after the review was completed.
10.	Other exclusion criteria	• Abstracts, conference presentations and theses • Non-human studies • Non-English language studies
11.	Context	There is currently no national guideline in the UK on the diagnosis and treatment of kidney cancer and audit data indicates variation in the clinical practice within NHS. Stakeholders identified this gap and NICE was commissioned to develop a guideline on kidney cancer by NHSE. There are various non-pharmacological (surgical and non-surgical) interventions for treating advanced RCC but their clinical benefit following SACT is uncertain. Therefore an evidence review is needed to evaluate the clinical and cost-effectiveness of these interventions in people with advanced RCC who have had previous treatment with SACT.
12.	Outcomes	• Progression-free survival (time to event data) • Overall survival (time to event data) Some studies may report overall survival as death or mortality. These will be extracted as an alternative related outcomes if overall survival is not reported (dichotomous data). • Cancer-specific survival (time to event data) If cancer specific survival is not reported, then cancer specific mortality (dichotomous data) will be extracted instead where available. • Severe adverse events reported as: o observed in the intraoperative period (measured according to Intraoperative Adverse Incident Classification – EAUiaiC; dichotomous data) o observed in the postoperative period (according to Clavien-Dindo Classification of Surgical Classifications at 30-days and 90-day period after surgery; dichotomous data) • Need for further systemic therapy, often expressed as the time-to-second line or further line of therapy (dichotomous or time to event data) • Number of hospital admissions (continuous data) • Duration of hospital stay (continuous data) • Quality of life using: o EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30; dichotomous or continuous data))

		EuroQol-5 dimensions (EQ-5D; dichotomous or continuous data) **Minimal important differences** Any statistically significant difference will be used for the following outcomes: ○ Survival outcomes ○ Severe adverse events ○ Quality of life using EORTC QLQ-C30 MIDs for the following quality of life measure was identified in the literature: EQ-5D: 0.08 for UK-based scores and 0.07 for VAS scores
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see section 6.2). Study investigators may be contacted for missing data where time and resources allow. This review may make use of the priority screening functionality within the EPPI-reviewer software. If priority screening is used the following rules will be adopted to determine when to stop screening: • at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) will be screened • After this point, screening is only terminated if a pre-specified threshold of 750 is met for a number of abstracts being screened without a single new include being identified.
14.	Risk of bias (quality) assessment	Risk of bias will be carried out using the preferred checklists as described in Appendix H of Developing NICE guidelines: the manual. The risk of bias for RCTs will be assessed using the Cochrane Risk of Bias v.2.0 checklist and for systematic reviews, the Risk of Bias in Systematic Reviews (ROBIS) tool will be used The risk of bias for non-RCT studies will be assessed using the Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool.
15.	Strategy for data synthesis	Where possible, meta-analyses will be conducted to combine the results of quantitative studies for each outcome. Where data can be disambiguated it will be separated into the subgroups identified in section 17 (below). Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. Continuous outcomes will be

		analysed as pooled mean differences (using the inverse variance method) unless multiple scales are used to measure the same factor. In these cases, standardised mean differences will be used instead. Where different studies present continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes will all converted to the same scale before meta-analysis is conducted on the mean differences. Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Hazard ratios will be pooled using the generic inverse-variance method. Adjusted, unadjusted and partially adjusted hazard ratios will be pooled. Sensitivity analysis will be carried out to look at the effect of removing partially and unadjusted studies For survival outcomes, time-to-event data is preferred. Where this data is not available, relative risks will be calculated for proxy outcomes as described in section 12. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all outcomes, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions are met: • Significant between-study heterogeneity in methodology, population, intervention, or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. GRADE will be used to assess the certainty of the outcomes. Data from randomised controlled trials and non-randomised comparative trials will be initially rated as high certainty where they come from: • RCTs and systematic reviews of RCTs (where individual studies have been quality assessed using Cochrane risk of bias) • non-randomised comparative trials and systematic reviews of non-randomised studies (where individual studies have been quality assessed using the ROBINS-I assessment tool) The quality of the evidence for each outcome will then be downgraded or not from this starting point based on the other GRADE domains.

		To assess imprecision, where there are no defined MIDs we will set the MID as the line of no effect for all outcomes except for (1.0 for dichotomous outcomes and 0 for continuous outcomes). A second decision threshold will be applied where the sample size is sufficiently small that it is not plausible any realistic effect size could have been detected. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias.
16.	Analysis of sub-groups	Where the data allows, subgroup analyses may be conducted to explore heterogeneity considering the following: • according to interventions received • according to line of SACT received previously • age • by primary RCC type e.g. clear cell, papillary, chromophobe • location of metastases • performance status of the person at baseline (e.g. ECOG and Karnofsky).
17.	Type and method of review	X Intervention Diagnostic Prognostic Qualitative Epidemiologic Service Delivery Other (please specify)
18.	Language	English
19.	Country	England
20.	Anticipated or actual start date	January 2025
21.	Anticipated completion date	March 2026
22.	Stage of review at time of this submission	

Review stage	**Started**	**Completed**
Preliminary searches		X
Piloting of the study selection process		X
Formal screening of search results against eligibility criteria		X
Data extraction		X
Risk of bias (quality) assessment		X
Data analysis		X

23.	Named contact	**Named contact** Centre for Guidelines, NICE **Named contact e-mail** kidneycancerguideline@nice.org.uk **Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team.
24.	Review team members	From the Guideline Development Team: • Steve Sharp, Technical adviser • Marie Harrisingh, Technical adviser • Sarah Boyce, Senior technical analyst • Fernando Zanghelini, Technical analyst • Olivia Crane, 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	Localised renal cell carcinoma, thermal ablation, stereotactic ablative radiotherapy, active surveillance
32.	Details of existing review of same topic by same authors	Not applicable
33.	Current review status	Ongoing Completed but not published X Completed and published Completed, published and being updated Discontinued
34.	Additional information	None
35.	Details of final publication	www.nice.org.uk

Effectiveness review protocol H2

ID	Field	Content
1.	Review title	Clinical and cost-effectiveness analysis of non-pharmacological interventions, used after systemic anti-cancer therapy for adults with advanced renal cell carcinoma.
2.	Review question	What is the clinical and cost-effectiveness of non-pharmacological interventions used after systemic anti-cancer therapy for adults with advanced renal cell carcinoma?
3.	Objective	To evaluate the clinical and cost effectiveness of non-surgical interventions used after previous systemic anti-cancer treatments (SACT) for adults with advanced renal cell carcinoma (RCC). The aim of this review is to identify where there may be clinical benefit in carrying out a surgical or non-surgical procedure after SACT.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • INAHTA For the economics review the following databases will be searched: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA Searches will be restricted by: • Date limitations: None • English language • Human studies • Abstracts, conference presentations and theses will be excluded The full search strategies will be published in the final review.
5.	Condition or domain being studied	Advanced renal cell carcinoma

6.	Population	Adults (18 years or over) with advanced RCC* who have previously received systemic anti-cancer treatment (SACT). *defined as metastatic/ advanced RCC or locally advanced inoperable RCC (histologically confirmed or suspected on imaging). Advanced RCC diagnosis confirmed according to the clinical or pathological TNM classification Exclusion: • Adults who have not received SACT previously. • Adults with localised or locally advanced disease that is considered to be operable. • Adults with advanced disease who are having palliative care only.
7.	Intervention	**Non-pharmacological procedures carried out after SACT to:** **Manage primary mass:** 1. Surgical interventions (where metastatic RCC is considered operable) • Cytoreductive nephrectomy in people without prior nephrectomy with or without surgical removal of lymph nodes (lymphadenectomy). 2. Non-surgical interventions • Stereotactic ablative radiotherapy (SABR) **Manage metastases:** 3. Surgical interventions • Surgical removal of metastases also known as metastasectomy (distinguish between complete and incomplete metastasectomy) 4. Non-surgical interventions • Thermal ablation including: ▪ Radiofrequency ablation ▪ Cryotherapy ▪ Microwave ablation • Radiotherapy: • External beam radiotherapy (EBRT) • Stereotactic ablative radiotherapy (SABR)
8.	Comparator	No non-pharmacological intervention before second or further-line SACT.
9.	Types of study to be included	• Systematic reviews of RCTs and RCTs are preferred where available for a comparison. • Where RCTs are not available for a comparison, systematic reviews of prospective and retrospective cohort studies and prospective and retrospective cohort studies will be considered.

		• Where good quality systematic reviews are identified, these may be used completely or as a source of references, depending on applicability. Alternatively, they may be updated by the addition of studies published after the review was completed.
10.	Other exclusion criteria	• Abstracts, conference presentations and theses • Non-human studies • Non-English language studies
11.	Context	There is currently no national guideline in the UK on the diagnosis and treatment of kidney cancer and audit data indicates variation in the clinical practice within NHS. Stakeholders identified this gap and NICE was commissioned to develop a guideline on kidney cancer by NHSE. There are various non-pharmacological (surgical and non-surgical) interventions for treating advanced RCC but their clinical benefit following SACT is uncertain. Therefore an evidence review is needed to evaluate the clinical and cost-effectiveness of these interventions in people with advanced RCC who have had previous treatment with SACT.
12.	Outcomes	• Progression-free survival (time to event data) • Overall survival (time to event data) Some studies may report overall survival as death or mortality. These will be extracted as an alternative related outcomes if overall survival is not reported (dichotomous data). • Cancer-specific survival (time to event data) If cancer specific survival is not reported, then cancer specific mortality (dichotomous data) will be extracted instead where available. • Severe adverse events reported as: o observed in the intraoperative period (measured according to Intraoperative Adverse Incident Classification – EAUiaiC; dichotomous data) o observed in the postoperative period (according to Clavien-Dindo Classification of Surgical Classifications at 30-days and 90-day period after surgery; dichotomous data) • Need for further systemic therapy, often expressed as the time-to-second line or further line of therapy (dichotomous or time to event data) • Number of hospital admissions (continuous data) • Duration of hospital stay (continuous data) • Quality of life using: o EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30; dichotomous or continuous data)) EuroQol-5 dimensions (EQ-5D; dichotomous or continuous data) **Minimal important differences** Any statistically significant difference will be used for the following outcomes:

		○ Survival outcomes ○ Severe adverse events ○ Quality of life using EORTC QLQ-C30 MIDs for the following quality of life measure was identified in the literature: EQ-5D: 0.08 for UK-based scores and 0.07 for VAS scores
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see section 6.2). Study investigators may be contacted for missing data where time and resources allow. This review may make use of the priority screening functionality within the EPPI-reviewer software. If priority screening is used the following rules will be adopted to determine when to stop screening: • at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) will be screened • After this point, screening is only terminated if a pre-specified threshold of 750 is met for a number of abstracts being screened without a single new include being identified.
14.	Risk of bias (quality) assessment	Risk of bias will be carried out using the preferred checklists as described in Appendix H of Developing NICE guidelines: the manual. The risk of bias for RCTs will be assessed using the Cochrane Risk of Bias v.2.0 checklist and for systematic reviews, the Risk of Bias in Systematic Reviews (ROBIS) tool will be used The risk of bias for non-RCT studies will be assessed using the Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool.
15.	Strategy for data synthesis	Where possible, meta-analyses will be conducted to combine the results of quantitative studies for each outcome. Where data can be disambiguated it will be separated into the subgroups identified in section 17 (below). Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. Continuous outcomes will be analysed as pooled mean differences (using the inverse variance method) unless multiple scales are used to measure the same factor. In these cases, standardised mean differences will be used instead. Where different studies present continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10

		and a 0-100 visual analogue scale), these outcomes will all converted to the same scale before meta-analysis is conducted on the mean differences. Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Hazard ratios will be pooled using the generic inverse-variance method. Adjusted, unadjusted and partially adjusted hazard ratios will be pooled. Sensitivity analysis will be carried out to look at the effect of removing partially and unadjusted studies For survival outcomes, time-to-event data is preferred. Where this data is not available, relative risks will be calculated for proxy outcomes as described in section 12. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all outcomes, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions are met: • Significant between-study heterogeneity in methodology, population, intervention, or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. GRADE will be used to assess the certainty of the outcomes. Data from randomised controlled trials and non-randomised comparative trials will be initially rated as certainty where they come from: • RCTs and systematic reviews of RCTs (where individual studies have been quality assessed using Cochrane risk of bias) • non-randomised comparative trials and systematic reviews of non-randomised studies (where individual studies have been quality assessed using the ROBINS-I assessment tool) The quality of the evidence for each outcome will then be downgraded or not from this starting point based on the other GRADE domains. To assess imprecision, where there are no defined MIDs we will set the MID as the line of no effect for all outcomes except for (1.0 for dichotomous outcomes and 0 for continuous outcomes). A second decision threshold will be applied where the sample size is sufficiently small that it is not plausible any realistic effect size could have been detected.

		Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias.
16.	Analysis of sub-groups	Where the data allows, subgroup analyses may be conducted to explore heterogeneity considering the following: • according to interventions received • according to line of SACT received previously • age • by primary RCC type e.g. clear cell, papillary, chromophobe • location of metastases • performance status of the person at baseline (e.g. ECOG and Karnofsky).
17.	Type and method of review	X Intervention Diagnostic Prognostic Qualitative Epidemiologic Service Delivery Other (please specify)
18.	Language	English
19.	Country	England
20.	Anticipated or actual start date	January 2025
21.	Anticipated completion date	December 2025
22.	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.
23.	Review team members	From the Guideline Development Team: • Steve Sharp, Technical adviser • Marie Harrisingh, Technical adviser • Sarah Boyce, Senior technical analyst • Fernando Zanghelini, Technical analyst • Olivia Crane, Technical analyst • Lindsay Claxton, Health economics adviser • Hannah Tebbs, Health economist • Yuanyuan Zhang, Health economist • Amy Finnegan, Senior Information specialist
24.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team which receives funding from NICE.

25.	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.
26.	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).
27.	Other registration details	None
28.	Reference/URL for published protocol	None
29.	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.
30.	Keywords	Localised renal cell carcinoma, thermal ablation, stereotactic ablative radiotherapy, active surveillance
31.	Details of existing review of same topic by same authors	Not applicable
32.	Current review status	X Ongoing Completed but not published Completed and published Completed, published and being updated Discontinued
33.	Additional information	None
34.	Details of final publication	www.nice.org.uk

Economic review protocol for management of renal cell carcinoma

Table 12: Economic review protocol

ID	Field	Content
1.	Review questions	A: Cost-effectiveness of partial versus radical nephrectomy in adults with localised renal cell carcinoma B: Cost-effectiveness of non-surgical interventions or active surveillance in adults with localised renal cell carcinoma C: Cost-effectiveness of nephrectomy or stereotactic ablative radiotherapy for treating locally advanced renal cell carcinoma in adults H1: Cost-effectiveness of non-pharmacological interventions, used before systemic anti-cancer therapy for adults with advanced renal cell carcinoma H2: Cost-effectiveness of non-pharmacological interventions, used after systemic anti-cancer therapy for adults with advanced renal cell carcinoma
2.	Objective	To identify economic studies for all relevant guideline review questions on the management of 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 all review questions relating to the management of renal cell carcinoma using guideline population-specific terms and a health economic study filter. For search details see appendix B below. The following databases will be searched: • MEDLINE All, Ovid • Embase, Ovid • International HTA database, International Network of Agencies for Health Technology Assessment (INAHTA) • Econlit • NHS EED and HTA (legacy records)
6.	Review strategy	• Studies meeting the inclusion and exclusion criteria will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist in appendix H of Developing NICE guidelines: the manual. • The NICE economic evaluation checklist assesses: ○ Applicability to the NICE guideline decision making context with consideration of the NICE reference case relevant to the guideline. Recent UK studies that use the NICE reference case methods are the most applicable when considering cost effectiveness. ○ Methodological limitations. • The aim is to present the best available economic evidence to inform committee decision-making in the context of the guideline, the current UK NHS setting and NICE methods. Therefore, the health economist may not present all studies that meet inclusion criteria. If recent high quality, UK cost-utility analyses are available for a question, it is often not deemed informative to present studies that are less applicable or lower quality such as older UK analyses or analyses from other countries. A similar principle is deemed to apply more generally when considering applicability and methodological limitations. Some specific examples are given below: ○ If multiple versions of a model are available for the UK and other countries it is usually reasonable to only present the UK version. ○ If multiple versions of the same UK model are available, it is usually reasonable to present only the most recent. ○ If there has been a NICE MTA or guideline model that informs current NHS practice it is usually reasonable not to present older

		studies, unless they address a different subpopulation or other specific issue. ○ If a UK model that includes all interventions in the decision space is available it may be reasonable not to present studies that only include individual or fewer interventions, if the analysis is sufficiently applicable and of good methodological quality. • Quality and relevance of effectiveness data used in the economic analysis: the more closely the clinical effectiveness data used in the economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. • Hierarchy of economic evaluation evidence based on quality assessment ○ 'Directly applicable' and 'Minor limitations' (only recent UK CUAs can get this rating). Usually presented and used in decision-making. ○ Directly or partially applicable combined with minor or potentially serious limitations (other than 1). Discretion over whether these are presented and used in decision-making, depending on the availability of more relevant evidence. ○ 'Not applicable' or 'Very serious limitations'. Typically not presented and not used in decision-making. The health economist will make a decision based on the relative applicability and quality of the available evidence for each question, in discussion with the guideline committee if required. All decisions will be transparently reported in the evidence report. Studies that are presented to the committee and used in decision-making when formulating recommendations will be included in the summary tables and will have an evidence extraction. Other studies may not be presented to the committee in detail but will be listed, with the reason for not being presented to the committee and thus not used in decision-making being provided. Committee members can review and query the decision not to present studies with the health economist and will be provided with full details of these studies where requested.

Appendix B – Literature search strategies

Background and development

Search design and peer review

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

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

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

Review management

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

Prior work

A test set of 8 systematic reviews were supplied by the technical analysts, this test set covered the current review (review H1 and H2) and reviews A, B, C (review A: surgical interventions for localised RCC, review B: non-surgical interventions for localised RCC and review C: nephrectomy or stereotactic ablative radiotherapy for locally advanced RCC).

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and 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.

Randomised controlled trials 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

The precise 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.

Key decisions

A single systematic search was carried out to identify potentially relevant studies for the current review (review H1 and H2) and reviews A, B, C (review A: surgical interventions for localised RCC, review B: non-surgical interventions for localised RCC and review C: nephrectomy or stereotactic ablative radiotherapy for locally advanced RCC).

Clinical searches

Database results

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	18/01/2024	Wiley	Issue 1 of 12, January 2024	767
Cochrane Database of Systematic Reviews (CDSR)	18/01/2024	Wiley	Issue 1 of 12, January 2024	8
Embase	18/01/2024	Ovid	1974 to 2024 January 18	13394
Epistemonikos	18/01/2024	Epistemonikos	n/a	1993
INAHTA	18/01/2024	INAHTA	n/a	97
MEDLINE ALL	18/01/2024	Ovid	1946 to January 17, 2024	9991

Rerun search database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	14/02/2025	Wiley	Issue 2 of 12, February 2025	845
Cochrane Database of Systematic Reviews (CDSR)	14/02/2025	Wiley	Issue 2 of 12, February 2025	8
Embase	14/02/2025	Ovid	1974 to 2025 February 13	14588
Epistemonikos	14/02/2025	Epistemonikos	n/a	2350
INAHTA	14/02/2025	INAHTA	n/a	177
MEDLINE ALL	14/02/2025	Ovid	1946 to February 13, 2025	10686

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

Search strategy history

Database name: Medline ALL

Searches
1 exp Kidney Neoplasms/ (85773) 2 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or stage-4)).ti,ab. (17162) 3 (collecting-duct* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4)).ti,ab. (490) 4 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti,ab. (70604) 5 (Kidney* adj2 (Transitional-cell* or cell or urothelial* or duct or advanc*) adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*)).ti,ab. (808) 6 or/1-5 (118618) 7 exp nephrectomy/ (37938) 8 (nephrectom* or lymphadenectom*).ti,ab,kw. (62205) 9 ((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*)).ti,ab. (204663) 10 ((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*) and (remov* or surg* or extract* or extirpat* or operat*)).kf. (59909) 11 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (918105) 12 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) and (surg* or remov* or partial* or procedur* or treat* or operat*)).kf. (21870) 13 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)).ti,ab. (2661) 14 (nephron* and (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)).kf. (446) 15 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/ (239644) 16 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or stereostat* or SABR).ti,ab,kw. (933898) 17 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (2177) 18 ((RAS or (robotic* adj1 assist*)) and (surg* or remov* or partial* or procedur* or treat* or operat*)).kw. (11) 19 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (38472) 20 (minimal* and invas* and (surg* or procedur* or treat*)).kw. (5) 21 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (279) 22 ((inferior-vena-cava or IVC) and thrombectom*).kw. (26)

Searches
23 ((activ* or tumo?r* or delay*) adj2 (surveil* or monitor*)).ti,ab. (38392) 24 ((activ* or tumo?r* or delay*) and (surveil* or monitor*)).kw. (266) 25 (delay* adj2 treat*).ti,ab. (20889) 26 (delay* and treat*).kw. (162) 27 (watchful* adj1 wait*).ti,ab. (3238) 28 (watchful* and wait*).kw. (4) 29 or/7-28 (2201330) 30 6 and 29 (38582) 31 animals/ not humans/ (5153512) 32 30 not 31 (36911) 33 limit 32 to english language (30806) 34 limit 33 to (letter or historical article or comment or editorial or news or case reports) (9081) 35 33 not 34 (21725) 36 exp Randomized Controlled Trial/ (608436) 37 randomi?ed.mp. (1099661) 38 placebo.mp. (252799) 39 or/36-38 (1166623) 40 (MEDLINE or pubmed).tw. (344612) 41 systematic review.tw. (287748) 42 systematic review.pt. (249879) 43 meta-analysis.pt. (193317) 44 intervention$.ti. (208375) 45 or/40-44 (719849) 46 Epidemiologic studies/ (9465) 47 exp case control studies/ (1474038) 48 exp cohort studies/ (2562056) 49 Case control.tw. (159034) 50 (cohort adj (study or studies)).tw. (337093) 51 Cohort analy$.tw. (12565) 52 (Follow up adj (study or studies)).tw. (57443) 53 (observational adj (study or studies)).tw. (171478) 54 Longitudinal.tw. (336148) 55 Retrospective.tw. (784597) 56 Cross sectional.tw. (542555) 57 Cross-sectional studies/ (489693) 58 or/46-57 (3917614) 59 39 or 45 or 58 (5240090) 60 35 and 59 (10204) 61 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

Searches
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/ (1322150) 62 "organisation for economic co-operation and development"/ (581) 63 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/ (3526314) 64 european union/ (17879) 65 developed countries/ (21470) 66 or/62-65 (3542495) 67 61 not 66 (1231834) 68 60 not 67 (9991)

Database name: Embase

Searches
1 exp kidney tumor/ (169289) 2 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or stage-4)).ti,ab. (25843) 3 (collecting-duct* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4)).ti,ab. (738) 4 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti,ab. (105763) 5 (Kidney* adj2 (Transitional-cell* or cell or urothelial* or duct or advanc*) adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*)).ti,ab. (1179) 6 or/1-5 (199212) 7 exp nephrectomy/ (79135) 8 (nephrectom* or lymphadenectom*).ti,ab,kw. (95869) 9 ((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*)).ti,ab. (296316) 10 ((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

Searches
malignan* or sarcoma* or hypernephroma* or nephrocarcinoma*) and (remov* or surg* or extract* or extirpat* or operat*)).kf. (84073) 11 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (1172497) 12 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) and (surg* or remov* or partial* or procedur* or treat* or operat*)).kf. (39682) 13 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)).ti,ab. (4849) 14 (nephron* and (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)).kf. (923) 15 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/ (700411) 16 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or stereostat* or SABR).ti,ab,kw. (1245790) 17 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (3847) 18 ((RAS or (robotic* adj1 assist*)) and (surg* or remov* or partial* or procedur* or treat* or operat*)).kw. (21) 19 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (58741) 20 (minimal* and invas* and (surg* or procedur* or treat*)).kw. (8) 21 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (642) 22 ((inferior-vena-cava or IVC) and thrombectom*).kw. (36) 23 ((activ* or tumo?r* or delay*) adj2 (surveil* or monitor*)).ti,ab. (56960) 24 ((activ* or tumo?r* or delay*) and (surveil* or monitor*)).kw. (432) 25 (delay* adj2 treat*).ti,ab. (32640) 26 (delay* and treat*).kw. (278) 27 (watchful* adj1 wait*).ti,ab. (4967) 28 (watchful* and wait*).kw. (8) 29 or/7-28 (3008790) 30 6 and 29 (72417) 31 nonhuman/ not human/ (5369703) 32 30 not 31 (70586) 33 limit 32 to english language (63135) 34 33 not (letter or editorial).pt. (61048) 35 34 not (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (41463) 36 random:.tw. (2023923) 37 placebo:.mp. (532136) 38 double-blind:.tw. (248720) 39 or/36-38 (2304835) 40 (MEDLINE or pubmed).tw. (428718) 41 exp systematic review/ or systematic review.tw. (533296) 42 meta-analysis/ (304008) 43 intervention$.ti. (274290) 44 or/40-43 (1007209) 45 Clinical study/ (165319) 46 Case control study/ (212430) 47 Family study/ (25771) 48 Longitudinal study/ (205110)

Searches
49 Retrospective study/ (1556506) 50 comparative study/ (1042643) 51 Prospective study/ (902470) 52 Randomized controlled trials/ (268035) 53 51 not 52 (891477) 54 Cohort analysis/ (1106561) 55 cohort analy$.tw. (20347) 56 (Cohort adj (study or studies)).tw. (487394) 57 (Case control$ adj (study or studies)).tw. (176315) 58 (follow up adj (study or studies)).tw. (75066) 59 (observational adj (study or studies)).tw. (266587) 60 (epidemiologic$ adj (study or studies)).tw. (124259) 61 (cross sectional adj (study or studies)).tw. (359262) 62 case series.tw. (152596) 63 prospective.tw. (1133006) 64 retrospective.tw. (1304827) 65 or/45-50,53-64 (5603678) 66 39 or 44 or 65 (7885322) 67 35 and 66 (13670) 68 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/ (1736652) 69 exp "organisation for economic co-operation and development"/ (2827) 70 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

Searches
south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ (3832351) 71 european union/ (31891) 72 developed country/ (35945) 73 or/69-72 (3866518) 74 68 not 73 (1580645) 75 67 not 74 (13394)

Database name: Cochrane CDSR & CENTRAL

Searches
#1 MeSH descriptor: [Kidney Neoplasms] explode all trees 1694 #2 (Kidney* NEAR/2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or stage-4)):ti,ab 1332 #3 (collecting-duct* NEAR/2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4)):ti,ab 14 #4 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumor* or renal-tumour* or grawitz-tumor* or grawitz-tumour* or hypernephroma* or nephrocarcinoma*):ti,ab 3747 #5 (Kidney* NEAR/2 (Transitional-cell* or cell or urothelial* or duct or advanc*) NEAR/2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*)):ti,ab 69 #6 {or #1-#5} 5140 #7 MeSH descriptor: [Nephrectomy] explode all trees 594 #8 (nephrectom* or lymphadenectom*):ti,ab 3676 #9 MeSH descriptor: [Radiotherapy] this term only 2824 #10 MeSH descriptor: [Lymphatic Irradiation] this term only 76 #11 MeSH descriptor: [Radiosurgery] this term only 485 #12 MeSH descriptor: [Radiotherapy, Adjuvant] this term only 1427 #13 MeSH descriptor: [Radiotherapy Dosage] this term only 2429 #14 MeSH descriptor: [Radiotherapy, High-Energy] this term only 320 #15 MeSH descriptor: [Re-Irradiation] this term only 37 #16 MeSH descriptor: [Cytoreduction Surgical Procedures] this term only 232 #17 MeSH descriptor: [Ablation Techniques] this term only 127 #18 MeSH descriptor: [Radiofrequency Ablation] this term only 342 #19 MeSH descriptor: [Robotic Surgical Procedures] this term only 716 #20 MeSH descriptor: [Minimally Invasive Surgical Procedures] this term only 1280 #21 MeSH descriptor: [Metastasectomy] this term only 43 #22 MeSH descriptor: [Lymph Node Excision] this term only 1540 #23 MeSH descriptor: [Watchful Waiting] this term only 469 #24 ((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*)):ti,ab 18334 #25 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) NEAR/3 (surg* or remov* or partial* or procedur* or treat* or operat*)):ti,ab 63782 #26 (nephron* NEAR/2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)):ti,ab 123 #27 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or stereostat* or SABR):ti,ab 63947 #28 ((RAS or (robotic* NEAR/1 assist*)) NEAR/1 (surg* or remov* or partial* or procedur* or treat* or operat*)):ti,ab 256 #29 (minimal* NEAR/2 invas* NEAR/2 (surg* or procedur* or treat*)):ti,ab 3606

Searches
#30 ((inferior-vena-cava or IVC) NEAR/2 thrombectom*):ti,ab 2 #31 ((activ* or tumor* or tumour* or delay*) NEAR/2 (surveil* or monitor*)):ti,ab 4050 #32 (delay* NEAR/2 treat*):ti,ab 2913 #33 (watchful* NEAR/1 wait*):ti,ab 668 #34 {or #7-#33} 150254 #35 #6 AND #34 1693 #36 "conference":pt or (clinicaltrials or trialsearch):so 725938 #37 #35 NOT #36 776

Database name: Epistemonikos

Searches
(kidney* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or stage-4 or (stage 1) or (stage 2) or (stage 3) or (stage 4))) OR (collecting-duct* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4 or (stage 1) or (stage 2) or (stage 3) or (stage 4))) OR ((collecting duct*) AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4 or (stage 1) or (stage 2) or (stage 3) or (stage 4))) OR (renal-cell* or (renal cell*) or rcc or ccrcc or renal-mass* or (renal mass*) or renal-tumor* or (renal tumor*) or renal-tumour* or (renal tumour*) or grawitz-tumor* or (grawitz tumor*) or grawitz-tumour* or (grawitz tumour*) or hypernephroma* or nephrocarcinoma*) OR (kidney* AND (transitional-cell* or (transitional cell*) or cell or urothelial* or duct or advanc*) AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*)) AND (nephrectom* or lymphadenectom*) OR ((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 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) AND (surg* or remov* or partial* or procedur* or treat* or operat*)) OR (nephron* AND (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)) OR (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or stereostat* or sabr) OR ((ras or (robotic* AND assist*)) AND (surg* or remov* or partial* or procedur* or treat* or operat*)) OR (minimal* AND invas* AND (surg* or procedur* or treat*)) OR ((inferior-vena-cava or ivc or (inferior vena cava)) AND thrombectom*) OR ((activ* or tumor* or tumour* or delay*) AND (surveil* or monitor*)) OR (delay* AND treat*) OR (watchful* AND wait*)

Database name: INAHTA

Searches
#1 "Kidney Neoplasms"[mhe] 111
#2 ((Kidney* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or

Searches
stage-4))) OR ((collecting-duct* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4)) OR ((renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumor* or renal-tumour* or grawitz-tumor* or grawitz-tumour* or hypernephroma* or nephrocarcinoma*)) OR ((Kidney* AND (Transitional-cell* or cell or urothelial* or duct or advanc*) AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*))) 105
#3 (((Kidney* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or stage-4))) OR ((collecting-duct* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4)) OR ((renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumor* or renal-tumour* or grawitz-tumor* or grawitz-tumour* or hypernephroma* or nephrocarcinoma*)) OR ((Kidney* AND (Transitional-cell* or cell or urothelial* or duct or advanc*) AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*)))) OR ("Kidney Neoplasms"[mhe]) 155
#4 "Nephrectomy"[mhe] 12
#5 ((nephrectom* or lymphadenectom*)) 31
#6 "Radiotherapy"[mh] 220
#7 "Lymphatic Irradiation"[mh] 0
#8 "Radiosurgery"[mh] 71
#9 "Radiotherapy Adjuvant"[mh] 27
#10 "Radiotherapy Dosage"[mh] 27
#11 "Radiotherapy High-Energy"[mh] 9
#12 "Re-Irradiation"[mh] 2
#13 "Cytoreduction Surgical Procedures"[mh] 2
#14 "Ablation Techniques"[mh] 35
#15 "Radiofrequency Ablation"[mh] 29
#16 "Robotic Surgical Procedures"[mh] 22
#17 "Minimally Invasive Surgical Procedures"[mh] 109
#18 "Metastasectomy"[mh] 1
#19 "Lymph Node Excision"[mh] 9
#20 ((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*)) 878
#21 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) AND (surg* or remov* or partial* or procedur* or treat* or operat*)) 756
#22 (nephron* AND (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)) 2
#23 radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or stereostat* or SABR) 1000
#24 ((RAS or (robotic* AND assist*)) AND (surg* or remov* or partial* or procedur* or treat* or operat*)) 73
#25 (minimal* AND invas* AND (surg* or procedur* or treat*))246

Searches		
#26	((inferior-vena-cava or IVC) AND thrombectom*)	0
#27	((activ* or tumor* or tumour* or delay*) AND (surveil* or monitor*))	318
#28	(delay* AND treat*)	201
#29	(watchful* AND wait*)	45
#29	#28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4	2796
#30	#29 AND #3	155
Limit	English language	97

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
EconLit	05/02/2024	OVID	1886 to January 25, 2024	1
EED	07/02/2024	CRD	n/a	23
Embase	05/02/2024	Ovid	1974 to 2024 February 02	65
HTA	07/02/2024	CRD	n/a	27
INAHTA	05/02/2024	INAHTA	n/a	155
MEDLINE ALL	05/02/2024	Ovid	1946 to February 02, 2024	62

Rerun search database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
EconLit	06/05/2025	OVID	1886 to May 01, 2025	1
Embase	06/05/2025	Ovid	1974 to 2025 May 05	73
INAHTA	06/05/2025	INAHTA	n/a	177
MEDLINE ALL	06/05/2025	Ovid	1946 to May 05, 2025	68

Search strategy history

Database name: Econlit

Searches
1 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or stage-4)).ti,ab. (8) 2 (collecting-duct* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4)).ti,ab. (0) 3 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti,ab. (22) 4 (Kidney* adj2 (Transitional-cell* or cell or urothelial* or duct or advanc*) adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*)).ti,ab. (0) 5 or/1-4 (30) 6 (nephrectom* or lymphadenectom*).ti,ab,kw. (0)

Searches
7 ((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*)).ti,ab. (80)
8 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (25798)
9 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)).ti,ab. (0)
10 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or stereostat* or SABR).ti,ab,kw. (599)
11 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (10)
12 ((RAS or (robotic* adj1 assist*)) and (surg* or remov* or partial* or procedur* or treat* or operat*)).kw. (0)
13 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (7)
14 (minimal* and invas* and (surg* or procedur* or treat*)).kw. (0)
15 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (0)
16 ((inferior-vena-cava or IVC) and thrombectom*).kw. (0)
17 ((activ* or tumo?r* or delay*) adj2 (surveil* or monitor*)).ti,ab. (388)
18 ((activ* or tumo?r* or delay*) and (surveil* or monitor*)).kw. (4)
19 (delay* adj2 treat*).ti,ab. (48)
20 (delay* and treat*).kw. (0)
21 (watchful* adj1 wait*).ti,ab. (10)
22 (watchful* and wait*).kw. (0)
23 or/6-22 (26909)
24 5 and 23 (1)

Database name: CRD EED & HTA

Searches

Line	Search	Hits
1	MESH DESCRIPTOR Kidney Neoplasms EXPLODE ALL TREES	201
2	(Kidney* NEAR2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or stage-4))	194
3	(collecting-duct* NEAR2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4))	1
4	(renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumor* or renal-tumour* or grawitz-tumor* or grawitz-tumour* or hypernephroma* or nephrocarcinoma*)	204
5	(Kidney* NEAR2 (Transitional-cell* or cell or urothelial* or duct or advanc*) NEAR2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*))	3
6	#1 OR #2 OR #3 OR #4 OR #5	262
7	MESH DESCRIPTOR Nephrectomy EXPLODE ALL TREES	95
8	(nephrectom* or lymphadenectom*)	235
9	MESH DESCRIPTOR Radiotherapy	247
10	MESH DESCRIPTOR Lymphatic Irradiation	1
11	MESH DESCRIPTOR Radiosurgery	125
12	MESH DESCRIPTOR Radiotherapy, Adjuvant	176
13	MESH DESCRIPTOR Radiotherapy Dosage	112
14	MESH DESCRIPTOR Radiotherapy, High-Energy	15
15	MESH DESCRIPTOR Re-Irradiation	0
16	MESH DESCRIPTOR Cytoreduction Surgical Procedures	4
17	MESH DESCRIPTOR Ablation Techniques	29
18	MESH DESCRIPTOR Radiofrequency Ablation	0
19	MESH DESCRIPTOR Robotic Surgical Procedures	23
20	MESH DESCRIPTOR Minimally Invasive Surgical Procedures	260
21	MESH DESCRIPTOR Metastasectomy	5
22	MESH DESCRIPTOR Lymph Node Excision	171
23	((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*) NEAR3 (remov* or surg* or extract* or extirpat* or operat*))	2281
24	((laproscop* or open or partial* or radical or transperiton* or retroperiton*) NEAR3 (surg* or remov* or partial* or procedur* or treat* or operat*))	1045
25	(nephron* NEAR2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*))	9
26	(radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or stereostat* or SABR)	3151
27	((RAS or (robotic* NEAR1 assist*)) NEAR1 (surg* or remov* or partial* or procedur* or treat* or operat*))	28
28	(minimal* NEAR2 invas* NEAR2 (surg* or procedur* or treat*))	425
29	((inferior-vena-cava or IVC) NEAR2 thrombectom*)	0
30	((activ* or tumor* or tumour* or delay*) NEAR2 (surveil* or monitor*))	119
31	(delay* NEAR2 treat*)	119
32	MESH DESCRIPTOR Watchful Waiting	38
33	(watchful* NEAR1 wait*)	137
34	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33	6388
35	#6 AND #34	97
36	(#35) IN NHSEED	23
37	(#35) IN HTA	27

Database name: Embase

Searches
1 exp kidney tumor/ (169657) 2 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or stage-4)).ti,ab. (25905) 3 (collecting-duct* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4)).ti,ab. (739) 4 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti,ab. (105980) 5 (Kidney* adj2 (Transitional-cell* or cell or urothelial* or duct or advanc*) adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*)).ti,ab. (1182) 6 or/1-5 (199645) 7 exp nephrectomy/ (79289) 8 (nephrectom* or lymphadenectom*).ti,ab,kw. (96024) 9 ((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*)).ti,ab. (296981) 10 ((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*) and (remov* or surg* or extract* or extirpat* or operat*)).kf. (84341) 11 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (1174471) 12 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) and (surg* or remov* or partial* or procedur* or treat* or operat*)).kf. (39794) 13 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)).ti,ab. (4849) 14 (nephron* and (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)).kf. (927) 15 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/ (702412) 16 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or stereostat* or SABR).ti,ab,kw. (1248256) 17 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (3873) 18 ((RAS or (robotic* adj1 assist*)) and (surg* or remov* or partial* or procedur* or treat* or operat*)).kw. (21) 19 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (58898) 20 (minimal* and invas* and (surg* or procedur* or treat*)).kw. (8) 21 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (647) 22 ((inferior-vena-cava or IVC) and thrombectom*).kw. (36)

Searches
23 ((activ* or tumo?r* or delay*) adj2 (surveil* or monitor*)).ti,ab. (57069) 24 ((activ* or tumo?r* or delay*) and (surveil* or monitor*)).kw. (432) 25 (delay* adj2 treat*).ti,ab. (32723) 26 (delay* and treat*).kw. (281) 27 (watchful* adj1 wait*).ti,ab. (4971) 28 (watchful* and wait*).kw. (8) 29 or/7-28 (3014855) 30 6 and 29 (72543) 31 nonhuman/ not human/ (5377221) 32 30 not 31 (70709) 33 limit 32 to english language (63258) 34 33 not (letter or editorial).pt. (61164) 35 34 not (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (41542) 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 vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ (1740991) 37 exp "organisation for economic co-operation and development"/ (2851) 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/ (3835523) 39 european union/ (31807) 40 developed country/ (35992) 41 or/37-40 (3869712)

Searches
42 36 not 41 (1584824) 43 35 not 42 (41050) 44 cost utility analysis/ (12696) 45 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. (30947) 46 ((incremental* adj2 cost*) or ICER).tw. (31650) 47 (cost adj2 utilit*).tw. (11338) 48 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. (3393) 49 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. (37671) 50 (cost and (effect* or utilit*)).ti. (58589) 51 or/44-50 (92726) 52 43 and 51 (65)

Database name: Medline ALL

Searches
1 exp Kidney Neoplasms/ (85968) 2 (Kidney* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or stage-4)).ti,ab. (17223) 3 (collecting-duct* adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4)).ti,ab. (491) 4 (renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumo?r* or grawitz-tumo?r* or hypernephroma* or nephrocarcinoma*).ti,ab. (70816) 5 (Kidney* adj2 (Transitional-cell* or cell or urothelial* or duct or advanc*) adj2 (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma*)).ti,ab. (817) 6 or/1-5 (118910) 7 exp nephrectomy/ (37965) 8 (nephrectom* or lymphadenectom*).ti,ab,kw. (62344) 9 ((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*)).ti,ab. (205263) 10 ((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*) and (remov* or surg* or extract* or extirpat* or operat*)).kf. (60200) 11 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) adj3 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (920508) 12 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) and (surg* or remov* or partial* or procedur* or treat* or operat*)).kf. (22001) 13 (nephron* adj2 (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)).ti,ab. (2662) 14 (nephron* and (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)).kf. (447) 15 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/ (240052)

Searches
16 (radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or stereostat* or SABR).ti,ab,kw. (936452) 17 ((RAS or (robotic* adj1 assist*)) adj1 (surg* or remov* or partial* or procedur* or treat* or operat*)).ti,ab. (2212) 18 ((RAS or (robotic* adj1 assist*)) and (surg* or remov* or partial* or procedur* or treat* or operat*)).kw. (11) 19 (minimal* adj2 invas* adj2 (surg* or procedur* or treat*)).ti,ab. (38673) 20 (minimal* and invas* and (surg* or procedur* or treat*)).kw. (5) 21 ((inferior-vena-cava or IVC) adj2 thrombectom*).ti,ab. (279) 22 ((inferior-vena-cava or IVC) and thrombectom*).kw. (26) 23 ((activ* or tumo?r* or delay*) adj2 (surveil* or monitor*)).ti,ab. (38554) 24 ((activ* or tumo?r* or delay*) and (surveil* or monitor*)).kw. (268) 25 (delay* adj2 treat*).ti,ab. (20957) 26 (delay* and treat*).kw. (163) 27 (watchful* adj1 wait*).ti,ab. (3243) 28 (watchful* and wait*).kw. (4) 29 or/7-28 (2207356) 30 6 and 29 (38664) 31 animals/ not humans/ (5159676) 32 30 not 31 (36990) 33 limit 32 to english language (30881) 34 limit 33 to (letter or historical article or comment or editorial or news or case reports) (9092) 35 33 not 34 (21789) 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/ (1325188) 37 "organisation for economic co-operation and development"/ (587) 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

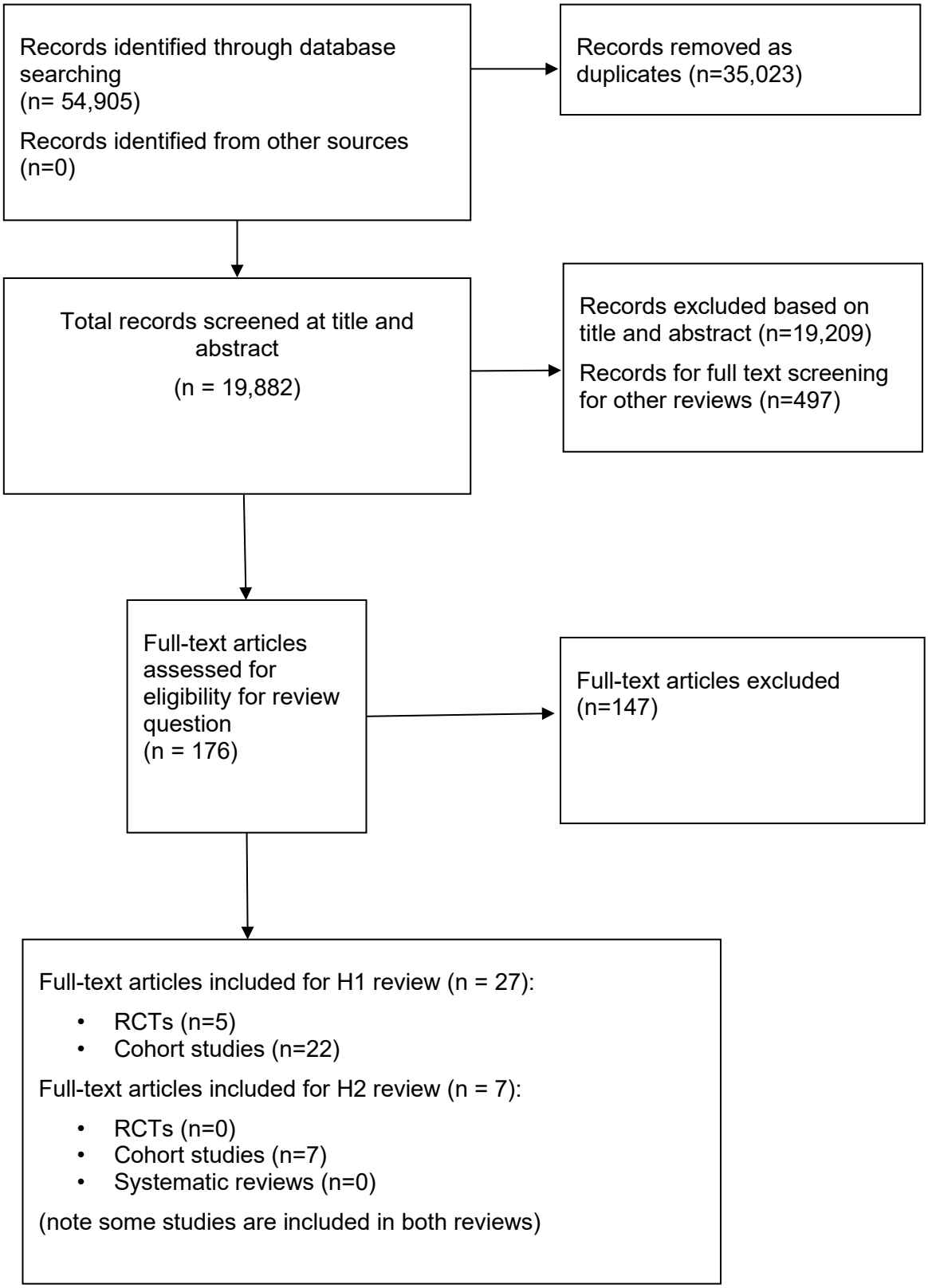
Searches
israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ (3530229) 39 european union/ (17894) 40 developed countries/ (21491) 41 or/37-40 (3546443) 42 36 not 41 (1234802) 43 35 not 42 (21490) 44 Cost-Benefit Analysis/ (93959) 45 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. (18159) 46 ((incremental* adj2 cost*) or ICER).tw. (18654) 47 (cost adj2 utilit*).tw. (7142) 48 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. (2429) 49 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. (24749) 50 (cost and (effect* or utilit*)).ti. (39941) 51 or/44-50 (116479) 52 43 and 51 (62)

Database name: INAHTA

Searches
#1 "Kidney Neoplasms"[mhe] 111 #2 ((Kidney* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumo?r* or mass or metastat* or malignan* or sarcoma* or parenchyma* or t1 or t1a or t1b or tb or t2a or t2b or t3 or t3a or t3b or t3c or stage-1 or stage-2 or stage-3 or stage-4))) OR ((collecting-duct* AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma* or stage-4)) OR ((renal-cell* or RCC or ccRCC or Renal-mass* or renal-tumor* or renal-tumour* or grawitz-tumor* or grawitz-tumour* or hypernephroma* or nephrocarcinoma*)) OR ((Kidney* AND (Transitional-cell* or cell or urothelial* or duct or advanc*) AND (cancer* or carcinoma* or carcinosarcoma* or adenocarcino* or neoplas* or tumor* or tumour* or mass or metastat* or malignan* or sarcoma* or parenchyma*))) 105 #3 #1 or #2 155 #4 "Nephrectomy"[mhe] 12 #5 ((nephrectom* or lymphadenectom*)) 31 #6 "Radiotherapy"[mh] 220 #7 "Lymphatic Irradiation"[mh] 0 #8 "Radiosurgery"[mh] 71 #9 "Radiotherapy Adjuvant"[mh] 27 #10 "Radiotherapy Dosage"[mh] 27 #11 "Radiotherapy High-Energy"[mh] 9 #12 "Re-Irradiation"[mh] 2 #13 "Cytoreduction Surgical Procedures"[mh] 2 #14 "Ablation Techniques"[mh] 35 #15 "Radiofrequency Ablation"[mh] 29 #16 "Robotic Surgical Procedures"[mh] 22

Searches
#17 "Minimally Invasive Surgical Procedures"[mh] 109
#18 "Metastasectomy"[mh] 1
#19 "Lymph Node Excision"[mh] 9
#20 ((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*)) 878
#21 ((laproscop* or open or partial* or radical or transperiton* or retroperiton*) AND (surg* or remov* or partial* or procedur* or treat* or operat*)) 756
#22 (nephron* AND (surg* or remov* or partial* or procedur* or treat* or operat* or spar* or preserv*)) 2
#23 radiotherap* or radiation* or radiosurg* or cyberknife* or irradiat* or thermoablat* or ablat* or cyrotherap* or cytoreduct* or cyroablat* or stereostat* or SABR) 1000
#24 ((RAS or (robotic* AND assist*)) AND (surg* or remov* or partial* or procedur* or treat* or operat*)) 73
#25 (minimal* AND invas* AND (surg* or procedur* or treat*))246
#26 ((inferior-vena-cava or IVC) AND thrombectom*) 0
#27 ((activ* or tumor* or tumour* or delay*) AND (surveil* or monitor*)) 318
#28 (delay* AND treat*) 201
#29 (watchful* AND wait*) 45
#30 "Watchful Waiting"[mh] 17
#31 #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 2803
#32 #31 AND #3 155

Appendix C – Effectiveness evidence study selection



Appendix D – Effectiveness evidence

Review 1 Cytoreductive nephrectomy then systemic anti-cancer therapy

Randomised controlled trials evidence

Bex, 2019

Bibliographic Reference	Bex, Axel; Mulders, Peter; Jewett, Michael; Wagstaff, John; van Thienen, Johannes V; Blank, Christian U; van Velthoven, Roland; Del Pilar Laguna, Maria; Wood, Lori; van Melick, Harm H E; Aarts, Maureen J; Lattouf, J B; Powles, Thomas; de Jong Md PhD, Igle Jan; Rottey, Sylvie; Tombal, Bertrand; Marreaud, Sandrine; Collette, Sandra; Collette, Laurence; Haanen, John; Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial.; JAMA oncology; 2019; vol. 5 (no. 2); 164-170

Study details

Other publications associated with this study included in review	Paper published by De Bruijn 2019 reported the duration of hospital stay from SURTIME trial
Trial registration number and/or trial name	SURTIME (NCT01099423)
Study type	Randomised Controlled Trial
Study location	Multicentre study with 19 institutions in the Netherlands, Belgium, the United Kingdom, and Canada
Study dates	This randomised clinical trial began on July 14, 2010, and continued until March 24, 2016, with a median follow-up of 3.3 years (range, 0-6.2 years) and a clinical cutoff date for this report of May 5, 2017.
Sources of funding	This study was supported by Pfizer and Kankerbestrijding/KWF from the Netherlands through the Cancer Research Fund of the European Organisation for Research and Treatment of Cancer
Inclusion criteria	People aged 18 years or older Histologically confirmed, previously untreated clear cell metastatic RCC

	Resectable asymptomatic primary tumour in situ Required therapy with sunitinib World Health Organization (WHO) performance status of 0 or 1 No clinical signs of central nervous system involvement A life expectancy greater than 3 months Adequate bone marrow, liver, cardiac, and renal function 3 or fewer surgical risk factors Measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1
Intervention(s)	Immediate cytoreductive nephrectomy followed by sunitinib therapy
Comparator	Treatment with 3 cycles of sunitinib followed by cytoreductive nephrectomy
Outcome measures	Progression-free survival Overall survival Severe adverse events
Number of participants	N = 99 Immediate cytoreductive nephrectomy + sunitinib = 50 Deferred cytoreductive nephrectomy + sunitinib = 49
Duration of follow-up	Median follow-up was 3.3 years (range, 0-6.2 years)
Loss to follow-up	Not reported
Methods of analysis	The trial originally aimed to test for a hazard ratio (HR) of 0.75 on PFS with a 2-sided, 5%-level log-rank test with 80% power. After 3 years of recruitment, accrual indicated that the study would not reach its planned objective. The secondary end points of PFS and OS were estimated by Kaplan-Meier analysis and compared in the ITT population using a Cox proportional hazards regression model stratified by WHO performance status.

Study arms

Immediate cytoreductive nephrectomy + sunitinib (N = 50)

Deferred cytoreductive nephrectomy+ sunitinib (N = 49)

Characteristics

Arm-level characteristics

Characteristic	Immediate cytoreductive nephrectomy + sunitinib (N = 50)	Deferred cytoreductive nephrectomy+ sunitinib (N = 49)
% Female No of events	n = 9 ; % = 18	n = 10 ; % = 20.4
Age Median (IQR)	60 (39 to 78)	58 (43 to 74)
Location of metastases - lung No of events	n = 43 ; % = 86	n = 42 ; % = 85.7
Location of metastases - bone No of events	n = 16 ; % = 32	n = 16 ; % = 32.6
Location of metastases - Adrenal gland No of events	n = 10 ; % = 20	n = 14 ; % = 28.6
Location of metastases - Liver No of events	n = 8 ; % = 16	n = 7 ; % = 14.3
Location of metastases - Other soft tissue No of events	n = 8 ; % = 16	n = 3 ; % = 6.1
Location of metastases - Malignant pleural effusion No of events	n = 5 ; % = 10	n = 0 ; % = 0
Location of metastases - Other site	n = 6 ; % = 12	n = 1 ; % = 2

Characteristic	Immediate cytoreductive nephrectomy + sunitinib (N = 50)	Deferred cytoreductive nephrectomy+ sunitinib (N = 49)
No of events		
Baseline performance status - WHO = 0 No of events	n = 36 ; % = 72	n = 31 ; % = 63.3
Baseline performance status - WHO = 1 No of events	n = 14 ; % = 38	n = 18 ; % = 36.7
MSKCC risk score - Intermediate risk (0-2 factors) No of events	n = 43 ; % = 86	n = 44 ; % = 89.8
MSKCC risk score - Poor risk (3 factors) No of events	n = 7 ; % = 14	n = 5 ; % = 10.2
Clinical T stage - T1 No of events	n = 9 ; % = 18	n = 8 ; % = 16.3
Clinical T stage - T2 No of events	n = 15 ; % = 30	n = 23 ; % = 46.9
Clinical T stage - T3 No of events	n = 22 ; % = 44	n = 15 ; % = 30.6
Clinical T stage - T4 No of events	n = 4 ; % = 8	n = 3 ; % = 6.1
Clinical N stage - N0 No of events	n = 17 ; % = 34	n = 20 ; % = 40.8
Clinical N stage - N1 No of events	n = 15 ; % = 30	n = 10 ; % = 20.4
Clinical N stage - N2 No of events	n = 10 ; % = 20	n = 8 ; % = 16.3

Characteristic	Immediate cytoreductive nephrectomy + sunitinib (N = 50)	Deferred cytoreductive nephrectomy+ sunitinib (N = 49)
Clinical N stage - Unknown No of events	n = 8 ; % = 16	n = 11 ; % = 22.5
Number of metastatic site - One No of events	n = 7 ; % = 14	n = 3 ; % = 6.1
Number of metastatic site - ≥ 2 No of events	n = 43 ; % = 86	n = 46 ; % = 93.9

Outcomes

Survival

Outcome	Deferred cytoreductive nephrectomy+ sunitinib vs Immediate cytoreductive nephrectomy + sunitinib, , N2 = 49, N1 = 50
Progression-free survival Hazard ratio/95% CI	0.88 (0.56 to 1.37)
Overall survival Hazard ratio/95% CI	0.57 (0.34 to 0.95)

Progression-free survival - Polarity - Higher values are better
Overall survival - Polarity - Higher values are better

Postoperative complications

Outcome	Immediate cytoreductive nephrectomy + sunitinib, , N = 46	Deferred cytoreductive nephrectomy+ sunitinib, , N = 34
Clavien-Dindo postoperative complications grade ≥ 3 No of events	n = 3 ; % = 6.5	n = 1 ; % = 2.9

Clavien-Dindo postoperative complications grade ≥ 3 - Polarity - Lower values are better

Critical appraisal – Cochrane Risk of Bias tool (RoB 2.0)

Question	Answer
Risk of bias judgement	Moderate *(Patients in the deferred group were allowed presurgical sunitinib dose modification)*
Overall Directness	Directly applicable

De Bruijn, 2019

Bibliographic Reference	De Bruijn, Roderick Emile; Mulders, Peter; Jewett, Michael A; Wagstaff, John; Van Thienen, Johan V; Blank, Christian U; Van Velthoven, Roland; Wood, Lori; van Melick, Harm E; Aarts, Maureen J; Lattouf, Jean B; Powles, Thomas; De Jong, Igle J; Rottey, Sylvie; Tombal, Betrand; Marreaud, Sandrine; Collette, Sandra; Collette, Laurence; Haanen, John B; Bex, Axel; Surgical Safety of Cytoreductive Nephrectomy Following Sunitinib: Results from the Multicentre, Randomised Controlled Trial of Immediate Versus Deferred Nephrectomy (SURTIME).; European urology; 2019; vol. 76 (no. 4); 437-440

Study details

Other publications associated with this study included in review	Paper published by Bexl, 2018 reported progression-free survival, overall survival outcomes from SURTIME trial
Trial registration number and/or trial name	SURTIME (NCT01099423)
Study type	Randomised Controlled Trial
Study location	Multicentre study with 19 institutions in the Netherlands, Belgium, the United Kingdom, and Canada
Study dates	This randomised clinical trial began on July 14, 2010, and continued until March 24, 2016.
Sources of funding	This study was supported by Pfizer and Kankerbestrijding/KWF from the Netherlands through the Cancer Research Fund of the European Organisation for Research and Treatment of Cancer
Inclusion criteria	People aged 18 years or older

	Histologically confirmed, previously untreated clear cell metastatic RCC Resectable asymptomatic primary tumour in situ Required therapy with sunitinib World Health Organization (WHO) performance status of 0 or 1 Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 No clinical signs of central nervous system involvement A life expectancy greater than 3 months Adequate bone marrow, liver, cardiac, and renal function 3 or fewer surgical risk factors
Intervention(s)	Immediate cytoreductive nephrectomy followed by sunitinib therapy
Comparator	Treatment with 3 cycles of sunitinib followed by cytoreductive nephrectomy
Outcome measures	Severe adverse events
Number of participants	N = 99 Immediate cytoreductive nephrectomy + sunitinib = 50 Deferred cytoreductive nephrectomy + sunitinib = 49 Analysis per protocol N = 74 Immediate cytoreductive nephrectomy + sunitinib = 40 Deferred cytoreductive nephrectomy + sunitinib = 34
Duration of follow-up	5.7 years
Loss to follow-up	Not reported
Methods of analysis	Surgical postoperative complication rates in both arms were reported as percentages with 95% confidence intervals.
Additional comments	

Study arms

Immediate cytoreductive nephrectomy+ sunitinib (Per Protocol) (N = 46)

Deferred cytoreductive nephrectomy+ sunitinib (Per Protocol) (N = 34)

Immediate cytoreductive nephrectomy+ sunitinib (N = 50)

Deferred cytoreductive nephrectomy+ sunitinib (N = 49)

Characteristics

Arm-level characteristics

Characteristic	Immediate cytoreductive nephrectomy+ sunitinib (Per Protocol) (N = 46)	Deferred cytoreductive nephrectomy+ sunitinib (Per Protocol) (N = 34)	Immediate cytoreductive nephrectomy+ sunitinib (N = 50)	Deferred cytoreductive nephrectomy+ sunitinib (N = 49)
% Female No of events	*empty data*	*empty data*	n = 9 ; % = 18	n = 10 ; % = 20
Age Median (IQR)	*empty data* (*empty data* to *empty data*)	*empty data* (*empty data* to *empty data*)	60 (39 to 78)	58 (43 to 74)
MSKCC risk score - Intermediate risk (0-2 factors) No of events	*empty data*	*empty data*	n = 43 ; % = 86	n = 44 ; % = 90
MSKCC risk score - Poor risk (3 factors) No of events	*empty data*	*empty data*	n = 7 ; % = 14	n = 5 ; % = 10
Clinical T stage - T1 No of events	*empty data*	*empty data*	n = 9 ; % = 18	n = 8 ; % = 16
Clinical T stage - T2 No of events	*empty data*	*empty data*	n = 15 ; % = 30	n = 23 ; % = 47

Characteristic	Immediate cytoreductive nephrectomy+ sunitinib (Per Protocol) (N = 46)	Deferred cytoreductive nephrectomy+ sunitinib (Per Protocol) (N = 34)	Immediate cytoreductive nephrectomy+ sunitinib (N = 50)	Deferred cytoreductive nephrectomy+ sunitinib (N = 49)
Clinical T stage - T3 No of events	*empty data*	*empty data*	n = 22 ; % = 44	n = 15 ; % = 31
Clinical T stage - T4 No of events	*empty data*	*empty data*	n = 4 ; % = 8	n = 3 ; % = 6
Clinical N stage - N0 No of events	*empty data*	*empty data*	n = 17 ; % = 34	n = 20 ; % = 41
Clinical N stage - N1 No of events	*empty data*	*empty data*	n = 15 ; % = 30	n = 10 ; % = 20
Clinical N stage - N2 No of events	*empty data*	*empty data*	n = 10 ; % = 20	n = 8 ; % = 16
Clinical N stage - Unknnown No of events	*empty data*	*empty data*	n = 8 ; % = 16	n = 11 ; % = 23
Number of metastatic site - One No of events	*empty data*	*empty data*	n = 7 ; % = 14	n = 3 ; % = 6
Number of metastatic site - ≥2 No of events	*empty data*	*empty data*	n = 43 ; % = 86	n = 46 ; % = 94

Outcomes

Duration of hospital stay

Outcome	Immediate cytoreductive nephrectomy+ sunitinib (Per Protocol), , N =	Deferred cytoreductive nephrectomy+ sunitinib (Per Protocol), , N =	Immediate cytoreductive nephrectomy+ sunitinib, , N = 46	Deferred cytoreductive nephrectomy+ sunitinib, , N = 34
Duration of hospital sta Mean (SD)	*empty data*	*empty data*	8.4 (7.1)	7.4 (3.4)

Duration of hospital sta - Polarity - Lower values are better

Critical appraisal –Cochrane Risk of Bias tool (RoB 2.0)

Question	Answer
Risk of bias judgement	Moderate *(Patients in the deferred group were allowed presurgical sunitinib dose modification)*
Overall Directness	Directly applicable

Mejean, 2021

Bibliographic Reference	Mejean, Arnaud; Ravaud, Alain; Thezenas, Simon; Chevreau, Christine; Bensalah, Karim; Geoffrois, Lionnel; Thiery-Vuillemin, Antoine; Cormier, Luc; Lang, Herve; Guy, Laurent; Gravis, Gwenaelle; Rolland, Frederic; Linassier, Claude; Lechevallier, Eric; Oudard, Stephane; Laguerre, Brigitte; Gross-Goupil, Marine; Bernhard, Jean Christophe; Colas, Sandra; Albiges, Laurence; Lebret, Thierry; Treluyer, Jean-Marc; Timsit, Marc-Olivier; Escudier, Bernard; Sunitinib Alone or After Nephrectomy for Patients with Metastatic Renal Cell Carcinoma: Is There Still a Role for Cytoreductive Nephrectomy?.; European urology; 2021; vol. 80 (no. 4); 417-424

Study details

Other publications associated with this study	CARMENA trial data has been published previously by Mejean A, 2018

included in review	
Trial registration number and/or trial name	CARMENA trial - NCT00930033
Study type	Randomised Controlled Trial
Study location	Multicentre - Not reported where the centres were based
Study dates	2009 to October 2018
Sources of funding	Funded by Assistance Publique–Hôpitaux de Paris and others
Inclusion criteria	Eastern Cooperative Oncology Group (ECOG) status score of 0 to 1 Patients with clear cell renal cell carcinoma confirmed on mandatory biopsy and documented metastatic disease Absence of brain metastases or treated brain metastases without recurrence 3 weeks after treatment Acceptable organ function
Exclusion criteria	Patients who received previous systemic treatment for kidney cancer (including VEGF-targeted therapy) or anticoagulants Patients with any medical condition, including cardiovascular disease, that ruled them out as candidates for treatment
Intervention(s)	Cytoreductive nephrectomy associated with sunitinib
Comparator	Sunitinib alone
Outcome measures	Overall survival
Number of participants	N = 450 Cytoreductive nephrectomy + sunitinib = 226 Sunitinib alone = 224
Duration of follow-up	36.6 months, cut-off (October 2018)
Loss to follow-up	There is 1(0.4%) missing patient in the CN + sunitinib arm
Methods of analysis	The overall survival analyses were estimated using the Kaplan-Meier method. Treatment arms were compared using a log-rank test. The post hoc analyses for efficacy were carried out on the intent to treat population.

	Treatment with sunitinib alone was considered to be non-inferior to cytoreductive nephrectomy followed by sunitinib treatment if the upper bound of the 95% CI of the HR for death was ≤1.20.

Study arms

Nephrectomy + sunitinib (ITT) (N = 226)

Sunitinib alone (ITT) (N = 224)

Characteristics

Arm-level characteristics

Characteristic	Nephrectomy + sunitinib (ITT) (N = 226)	Sunitinib alone (ITT) (N = 224)
% Female No of events	n = 57 ; % = 25.2	n = 57 ; % = 35.4
Age Median (IQR)	63 (33 to 84)	62 (30 to 87)
Location of metastases - lung No of events	n = 172 ; % = 79.3	n = 161 ; % = 72.9
Location of metastases - bone No of events	n = 78 ; % = 35.9	n = 82 ; % = 37.1
Location of metastases - Lymph nodes No of events	n = 76 ; % = 35	n = 86 ; % = 38.9
Location of metastases - Other No of events	n = 78 ; % = 35.9	n = 90 ; % = 40.7
Baseline performance status - ECOG 0 No of events	n = 130 ; % = 57.5	n = 122 ; % = 54.5
Baseline performance status - ECOG 1 No of events	n = 96 ; % = 42.5	n = 102 ; % = 45.5
Tumour stage - T1	n = 5 ; % = 7.5	n = 7 ; % = 14.3

Characteristic	Nephrectomy + sunitinib (ITT) (N = 226)	Sunitinib alone (ITT) (N = 224)
No of events		
Tumour stage - T2 No of events	n = 13 ; % = 19.4	n = 13 ; % = 26.5
Tumour stage - T3 or T4 No of events	n = 47 ; % = 70.1	n = 25 ; % = 51
Tumour stage - Tx No of events	n = 2 ; % = 3	n = 4 ; % = 8.2
MSKCC risk category - Intermediate risk No of events	n = 125 ; % = 55.6	n = 131 ; % = 58.5
MSKCC risk category - Poor risk No of events	n = 100 ; % = 44.4	n = 93 ; % = 41.5
Node stage - N0 No of events	n = 23 ; % = 34.8	n = 18 ; % = 36.7
Node stage - N1 No of events	n = 13 ; % = 19.7	n = 6 ; % = 12.2
Node stage - N2 No of events	n = 7 ; % = 10.6	n = 13 ; % = 26.5
Node stage - Nx No of events	n = 23 ; % = 34.8	n = 12 ; % = 24.5

Outcomes

Survival

Outcome	Sunitinib alone (ITT) vs Nephrectomy + sunitinib (ITT), , N2 = 224, N1 = 226
Overall survival Hazard ratio/95% CI	0.97 (0.79 to 1.19)

Overall survival - Polarity - Higher values are better

Critical appraisal –Cochrane Risk of Bias tool (RoB 2.0)

Question	Answer
Risk of bias judgement	Moderate *(There is some concern related to the unclear randomisation process)*
Overall Directness	Directly applicable

Mejean, 2018

Bibliographic Reference	Mejean, Arnaud; Ravaud, Alain; Thezenas, Simon; Colas, Sandra; Beauval, Jean-Baptiste; Bensalah, Karim; Geoffrois, Lionnel; Thiery-Vuillemin, Antoine; Cormier, Luc; Lang, Herve; Guy, Laurent; Gravis, Gwenaelle; Rolland, Frederic; Linassier, Claude; Lechevallier, Eric; Beisland, Christian; Aitchison, Michael; Oudard, Stephane; Patard, Jean-Jacques; Theodore, Christine; Chevreau, Christine; Laguerre, Brigitte; Hubert, Jacques; Gross-Goupil, Marine; Bernhard, Jean-Christophe; Albiges, Laurence; Timsit, Marc-Olivier; Lebret, Thierry; Escudier, Bernard; Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma.; The New England journal of medicine; 2018; vol. 379 (no. 5); 417-427

Study details

Trial registration number and/or trial name	CARMENA trial - NCT00930033
Study type	Randomised Controlled Trial
Study location	Multicentre - Not reported where the centres were based
Study dates	2009-2017
Sources of funding	Funded by Assistance Publique–Hôpitaux de Paris and others
Inclusion criteria	Eastern Cooperative Oncology Group (ECOG) status score of 0 to 1 Patients with clear cell renal cell carcinoma confirmed on mandatory biopsy and documented metastatic disease Absence of brain metastases or treated brain metastases without recurrence 3 weeks after treatment Acceptable organ function

Exclusion criteria	Patients who received previous systemic treatment for kidney cancer (including VEGF-targeted therapy) or anticoagulants Patients with any medical condition, including cardiovascular disease, that ruled them out as candidates for treatment
Intervention(s)	Cytoreductive nephrectomy associated with sunitinib
Comparator	Sunitinib alone
Outcome measures	Progression-free survival Severe adverse events
Number of participants	N = 450 Cytoreductive nephrectomy + sunitinib = 226 Sunitinib alone = 224
Duration of follow-up	50.9 months, at the time of data cutoff (December 12, 2017)
Loss to follow-up	Not reported
Methods of analysis	The rates and 95% confidence intervals for the analyses of overall survival and progression-free survival were estimated by the Kaplan–Meier method in the intention-to-treat population. Tumour response and safety data were analysed in patients who received sunitinib.

Study arms

Nephrectomy + sunitinib (N = 226)

Sunitinib alone (N = 224)

Characteristics

Arm-level characteristics

Characteristic	Nephrectomy + sunitinib (N = 226)	Sunitinib alone (N = 224)
% Female No of events	n = 57 ; % = 25.2	n = 57 ; % = 35.4
Age Median (IQR)	63 (33 to 84)	62 (30 to 87)
Location of metastases - Lung No of events	n = 172 ; % = 79.3	n = 161 ; % = 72.9

Characteristic	Nephrectomy + sunitinib (N = 226)	Sunitinib alone (N = 224)
Location of metastases - bone No of events	n = 78 ; % = 35.9	n = 82 ; % = 37.1
Location of metastases - Lymph nodes No of events	n = 76 ; % = 35	n = 86 ; % = 38.9
Location of metastases - Other No of events	n = 78 ; % = 35.9	n = 90 ; % = 40.7
Baseline performance status - ECOG 0 No of events	n = 130 ; % = 57.5	n = 122 ; % = 54.5
Baseline performance status - ECOG 1 No of events	n = 92 ; % = 42.5	n = 102 ; % = 45.3
Tumour stage - T1 No of events	n = 5 ; % = 7.5	n = 7 ; % = 14.3
Tumour stage - T2 No of events	n = 13 ; % = 19.4	n = 13 ; % = 26.5
Tumour stage - T3 or T4 No of events	n = 47 ; % = 70.1	n = 25 ; % = 51
Tumour stage - Tx No of events	n = 2 ; % = 3	n = 4 ; % = 8.2
MSKCC risk category - Intermediate risk No of events	n = 125 ; % = 55.6	n = 131 ; % = 58.5
MSKCC risk category - Poor risk No of events	n = 100 ; % = 44.4	n = 93 ; % = 41.5
Node stage - N0 No of events	n = 23 ; % = 34.8	n = 18 ; % = 36.7

Characteristic	Nephrectomy + sunitinib (N = 226)	Sunitinib alone (N = 224)
Node stage - N1 No of events	n = 13 ; % = 19.7	n = 6 ; % = 12.2
Node stage - N2 No of events	n = 7 ; % = 10.6	n = 13 ; % = 26.5
Node stage - Nx No of events	n = 23 ; % = 34.8	n = 12 ; % = 24.5

Outcomes

Survival

Outcome	Sunitinib alone vs Nephrectomy + sunitinib, , N2 = 224, N1 = 226
Progression-free survival Hazard ratio/95% CI	0.82 (0.67 to 1)

Progression-free survival - Polarity - Higher values are better

Adverse events

Outcome	Nephrectomy + sunitinib, , N = 186	Sunitinib alone, , N = 213
Any adverse event of grade 3 or 4 (Clavien Dindo) No of events	n = 61 ; % = 32.8	n = 91 ; % = 42.7

Any adverse event of grade 3 or 4 (Clavien Dindo) - Polarity - Lower values are better

Critical appraisal –Cochrane Risk of Bias tool (RoB 2.0)

Question	Answer
Risk of bias judgement	Moderate *(There is some concern related to the unclear randomisation process)*
Overall Directness	Directly applicable

Shen, 2023

Bibliographic Reference	Shen, X-P; Xie, M; Wang, J-S; Guo, X; Efficacy of immunotherapy-based immediate cytoreductive nephrectomy vs. deferred cytoreductive nephrectomy in metastatic renal cell carcinoma.; European review for medical and pharmacological sciences; 2023; vol. 27 (no. 12); 5684-5691

Study details

Study type	Randomised Controlled Trial
Study location	China
Study dates	2018 to 2020
Sources of funding	Not received.
Inclusion criteria	Histologically or cytologically confirmed clear cell renal cell carcinoma measurable disease according to RECIST 1.1 criteria, including primary and metastatic lesions Eastern Cooperative Oncology Group (ECOG) status score of 0 to 1 Life expectancy > 24 weeks Primary resectable tumour at first diagnosis
Exclusion criteria	Brain or liver metastases Poor prognosis as defined by Memorial Sloan-Kettering Cancer Center (MSKCC) or Heng criteria Severe hepatic or renal insufficiency or uncontrolled hypertension or diabetes mellitus Active infection Primary tumors from other sites Previous surgical or systemic treatment for metastatic renal cell carcinoma
Intervention(s)	Immediate cytoreductive nephrectomy
Comparator	Delayed cytoreductive nephrectomy
Outcome measures	Progression-free survival Overall survival
Number of participants	N = 84

	Immediate cytoreductive nephrectomy = 42 Delayed cytoreductive nephrectomy = 42
Duration of follow-up	Patients were followed up for 10-52 months, with a median follow-up period of 40.50 months.
Loss to follow-up	Not reported
Methods of analysis	Count data were expressed as rates (%), and differences between groups were compared using the Chi-square test. Survival data were expressed using the Kaplan Meier test.

Study arms

Immediate cytoreductive nephrectomy (N = 42)

Delayed cytoreductive nephrectomy (N = 42)

Characteristics

Arm-level characteristics

Characteristic	Immediate cytoreductive nephrectomy (N = 42)	Delayed cytoreductive nephrectomy (N = 42)
% Female No of events	n = 10 ; % = 23.8	n = 14 ; % = 33.3
Age Mean (SD)	65.58 (11.52)	61.29 (14.36)
TNM classification - T3a No of events	n = 22 ; % = 52.4	n = 18 ; % = 42.9
TNM classification - T3b No of events	n = 10 ; % = 23.8	n = 14 ; % = 33.3
TNM classification - T3c No of events	n = 5 ; % = 11.9	n = 6 ; % = 14.3
TNM classification - T4 No of events	n = 5 ; % = 11.9	n = 4 ; % = 9.5
Baseline performance status - ECOG 0 No of events	n = 29 ; % = 69.04	n = 24 ; % = 57.1

Characteristic	Immediate cytoreductive nephrectomy (N = 42)	Delayed cytoreductive nephrectomy (N = 42)
Baseline performance status - ECOG 1 No of events	n = 13 ; % = 31	n = 12 ; % = 42.9

Outcomes

Survival

Outcome	Delayed cytoreductive nephrectomy vs Upfrontcytoreductive nephrectomy, , N2 = 42, N1 = 42
Progression-free survival Hazard ratio/95% CI	0.53 (0.28 to 0.99)
Overall survival Hazard ratio/95% CI	0.81 (0.41 to 1.61)

Progression-free survival - Polarity - Higher values are better
Overall survival - Polarity - Higher values are better

Critical appraisal –Cochrane Risk of Bias tool (RoB 2.0)

Question	Answer
Risk of bias judgement	Moderate *(There is some concern related to the unclear randomisation process, also, there is no information on whether the trial analysis was performed in accordance with a pre-specified plan)*
Overall Directness	Directly applicable

Non-randomised controlled trials evidence

Bakouny, 2023

Bibliographic Reference	Bakouny, Ziad; El Zarif, Talal; Dudani, Shaan; Connor Wells, J; Gan, Chun Loo; Donskov, Frede; Shapiro, Julia; Davis, Ian D; Parnis, Francis; Ravi, Praful; Steinharter, John A; Agarwal, Neeraj; Alva, Ajjai; Wood, Lori; Kapoor, Anil; Ruiz Morales, Jose M; Kollmannsberger, Christian; Beuselinck, Benoit; Xie, Wanling; Heng, Daniel Y C; Choueiri, Toni K; Upfront Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma

Treated with Immune Checkpoint Inhibitors or Targeted Therapy: An Observational Study from the International Metastatic Renal Cell Carcinoma Database Consortium.; European urology; 2023; vol. 83 (no. 2); 145-151

Study details

Study type	Retrospective cohort study
Study location	US - uses the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) database
Study dates	January 2020
Sources of funding	None
Inclusion criteria	Treated with a first-line immune checkpoint inhibitor (including monotherapy and combination therapy with other immune check-point inhibitors or other agents) or targeted therapy regimen Initiated first-line systemic therapy on or after January 1, 2009 Diagnosed with de novo metastatic renal cell carcinoma or had not received a nephrectomy for localised renal cell carcinoma
Exclusion criteria	Missing dates of diagnosis or dates of metastatic disease Missing information on whether they had a nephrectomy or the date of nephrectomy Missing dates of death or last follow-up
Intervention(s)	Immune checkpoint inhibitors with upfront cytoreductive nephrectomy
Comparator	Immune checkpoint inhibitors no upfront cytoreductive nephrectomy
Outcome measures	Overall survival
Number of participants	N = 437 Immune checkpoint inhibitors with upfront cytoreductive nephrectomy = 234 Immune checkpoint inhibitors no upfront cytoreductive nephrectomy = 203
Duration of follow-up	The median follow-up for surviving patients treated with immune checkpoint inhibitors was 12 months.

Methods of analysis	For overall survival, the Kaplan-Meier methodology was used to summarise the survival distribution, and median overall survival and 95% confidence intervals (95% CIs) were computed. A multivariable logistic regression model with receipt of cytoreductive nephrectomy as the dependent variable (cytoreductive nephrectomy versus no cytoreductive nephrectomy), with the predictor variables chosen a priori: age (<65, 65–74, or >75 yr); presence of bone, brain, or liver metastases (yes or no); non– clear cell or sarcomatoid histology (yes or no); Karnofsky Performance Scale (KPS: ≥80 or <80); and the number of IMDC risk factors (≤1, 2, 3, or ≥4). Cox regressions were computed in each treatment group separately to determine the relationship between the receipt of cytoreductive nephrectomy and overall survival.
Additional comments	This study also reported results for people who received targeted therapy and upfront nephrectomy compared with targeted therapy only. These results are not extracted as there are reported in another study (Bhindi 2020).

Study arms

Immune checkpoint inhibitors with upfront cytoreductive nephrectomy (N = 234)

Immune checkpoint inhibitors no upfront cytoreductive nephrectomy (N = 203)

Characteristics

Arm-level characteristics

Characteristic	Immune checkpoint inhibitors with upfront cytoreductive nephrectomy (N = 234)	Immune checkpoint inhibitors no upfront cytoreductive nephrectomy (N = 203)
% Female No of events	n = 61 ; % = 26	n = 57 ; % = 28
Age Median (IQR)	60 (53 to 66)	63 (56 to 70)
Primary RCC type - Clear cell No of events	n = 204 ; % = 89	n = 110 ; % = 73
Primary RCC type - Non–clear cell No of events	n = 26 ; % = 11	n = 41 ; % = 27

Characteristic	Immune checkpoint inhibitors with upfront cytoreductive nephrectomy (N = 234)	Immune checkpoint inhibitors no upfront cytoreductive nephrectomy (N = 203)
IMDC - Favorable (0 risk factor) No of events	n = 18 ; % = 9	n = 1 ; % = 0.6
IMDC - Intermediate (1–2 risk factors) No of events	n = 143 ; % = 72	n = 78 ; % = 47
IMDC - Poor (3 risk factors) No of events	n = 39 ; % = 19	n = 88 ; % = 53
Sites of metastasis - One No of events	n = 52 ; % = 23	n = 39 ; % = 20
Sites of metastasis - ≥2 No of events	n = 171 ; % = 77	n = 155 ; % = 80
Presence of bone, brain, or liver metastases - Yes No of events	n = 87 ; % = 45	n = 120 ; % = 71
Presence of bone, brain, or liver metastases - No No of events	n = 108 ; % = 55	n = 48 ; % = 29

Outcomes

Survival

Outcome	Immune checkpoint inhibitors with upfront cytoreductive nephrectomy vs Immune checkpoint inhibitors no upfront cytoreductive nephrectomy , , N2 = 203, N1 = 234
Overall survival Hazard ratio/95% CI	0.61 (0.41 to 0.9)

Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest)*
Directness	Directly applicable

Bhindi, 2018

Bibliographic Reference	Bhindi, B.; Habermann, E.B.; Mason, R.J.; Costello, B.A.; Pagliaro, L.C.; Thompson, R.H.; Leibovich, B.C.; Boorjian, S.A.; Comparative Survival following Initial Cytoreductive Nephrectomy versus Initial Targeted Therapy for Metastatic Renal Cell Carcinoma; Journal of Urology; 2018; vol. 200 (no. 3); 528-534

Study details

Study type	Retrospective cohort study
Study location	US - uses national clinical oncology (NCDB) database
Study dates	2006 and 2013
Sources of funding	Not reported
Inclusion criteria	Metastatic patients at diagnosis
Exclusion criteria	Another prior cancer history NonRCC or unknown histology Missing vital status or follow-up Renal ablative procedure Inability to determine cytoreductive nephrectomy status Missing time to surgery in patients who underwent cytoreductive nephrectomy Missing time to targeted therapy in those who received targeted therapy No treatment (cytoreductive nephrectomy or targeted therapy) within 3 months of diagnosis

Intervention(s)	Initial cytoreductive nephrectomy + targeted therapy
Comparator	Initial targeted therapy + cytoreductive nephrectomy
Outcome measures	Overall survival
Number of participants	N = 15,068 Initial cytoreductive nephrectomy + targeted therapy = 6,731 Initial targeted therapy + cytoreductive nephrectomy = 8,337
Duration of follow-up	Median follow-up in survivors was 31 months (IQR 19-50)
Methods of analysis	Overall survival was compared between the initial cytoreductive nephrectomy and initial targeted therapy groups using Kaplan-Meier analysis and Cox regression models with censoring at end of the study period or due to loss to follow-up. To account for differences in baseline characteristics which may have influenced the initial treatment selection the author performed inverse probability of treatment weighting based on the propensity to receive initial cytoreductive nephrectomy vs initial targeted therapy, which was in turn estimated by logistic regression. Included variables in the inverse probability of treatment weighting were: age, sex, race/ethnicity, year of diagnosis, insurance status, income quartile, education, county of residence, Charlson-Deyo score, facility location, facility type, histology, clinical T-stage, and clinical N-stage
Additional comments	

Study arms

Initial cytoreductive nephrectomy + targeted therapy (N = 6731)

Initial targeted therapy + cytoreductive nephrectomy (N = 8337)

Characteristics

Arm-level characteristics

Characteristic	Initial cytoreductive nephrectomy + targeted therapy (N = 6731)	Initial targeted therapy + cytoreductive nephrectomy (N = 8337)
% Female No of events	n = 2081 ; % = 30.9	n = 2581 ; % = 31

Characteristic	Initial cytoreductive nephrectomy + targeted therapy (N = 6731)	Initial targeted therapy + cytoreductive nephrectomy (N = 8337)
Primary RCC type - clear cell No of events	n = 3647 ; % = 54.2	n = 2727 ; % = 32.7
Primary RCC type - Non–clear cell No of events	n = 817 ; % = 12.1	n = 600 ; % = 7.2
Primary RCC type - RCC, unknown subtype No of events	n = 2267 ; % = 33.7	n = 5010 ; % = 60.1
Clinical T-stage - cT1 No of events	n = 1024 ; % = 15.2	n = 1513 ; % = 18.2
Clinical T-stage - cT2 No of events	n = 1812 ; % = 26.9	n = 1735 ; % = 20.8
Clinical T-stage - cT3 No of events	n = 2503 ; % = 37.2	n = 1903 ; % = 22.8
Clinical T-stage - cT4 No of events	n = 488 ; % = 7.2	n = 990 ; % = 11.9
Clinical T-stage - cTx No of events	n = 904 ; % = 13.4	n = 2196 ; % = 26.3
Clinical N-stage - cN0 No of events	n = 3872 ; % = 57.5	n = 3328 ; % = 39.9
Clinical N-stage - cN1 No of events	n = 1701 ; % = 25.3	n = 2935 ; % = 35.2
Clinical N-stage - cNx No of events	n = 1158 ; % = 17.2	n = 2074 ; % = 24.9

Outcomes

Survival

Outcome	Initial cytoreductive nephrectomy + targeted therapy vs Initial targeted therapy + cytoreductive nephrectomy, , N2 = 6731, N1 = 8337
Overall survival - Entire mRCC cohort Hazard ratio/95% CI	0.62 (0.59 to 0.65)
Overall survival - Clear cell RCC subset Hazard ratio/95% CI	0.61 (0.58 to 0.65)
Overall survival - Nonclear cell RCC subset Hazard ratio/95% CI	0.73 (0.64 to 0.84)

Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest)*
Directness	Directly applicable

Bhindi, 2020

Bibliographic Reference	Bhindi, Bimal; Graham, Jeffrey; Wells, J Connor; Bakouny, Ziad; Donskov, Frede; Fraccon, Anna; Pasini, Felice; Lee, Jae Lyun; Basappa, Naveen S; Hansen, Aaron; Kollmannsberger, Christian K; Kanesvaran, Ravindran; Yuasa, Takeshi; Ernst, D Scott; Srinivas, Sandy; Rini, Brian I; Bowman, Isaac; Pal, Sumanta K; Choueiri, Toni K; Heng, Daniel Y C; Deferred Cytoreductive Nephrectomy in Patients with Newly Diagnosed Metastatic Renal Cell Carcinoma.; European urology; 2020; vol. 78 (no. 4); 615-623

Study details

Study type	Retrospective cohort study
Study location	33 centres in Canada, the USA, Belgium, Denmark, Germany, Greece, Italy, South Korea, Singapore, Japan, New Zealand, and Australia

Study dates	2006-2018
Sources of funding	None
Inclusion criteria	Only patients whose first systemic therapy was sunitinib
Exclusion criteria	Missing data on confounder variables First treatment (sunitinib or upfront cytoreductive nephrectomy) >12 months after diagnosis A period of surveillance of >6 months after upfront cytoreductive nephrectomy Unknown timing of deferred cytoreductive nephrectomy
Intervention(s)	Upfront cytoreductive nephrectomy + sunitinib
Comparator	Sunitinib + deferred cytoreductive nephrectomy
Outcome measures	Overall survival
Number of participants	N = 1,541 Upfront cytoreductive nephrectomy + sunitinib N = 805 Sunitinib + deferred cytoreductive nephrectomy N = 85 Sunitinib alone N = 651
Duration of follow-up	Median follow-up among survivors from first treatment initiation was 25 months (IQR 10–49)
Methods of analysis	Survival curves were plotted using the Kaplan-Meier method in order to describe benchmark OS outcomes, and were compared using the log-rank test. Multivariable Cox proportional hazards models were created including the following a priori selected potential confounders: upfront cytoreductive nephrectomy and deferred cytoreductive nephrectomy, age at diagnosis (continuous), sex, year of diagnosis (continuous), Karnofsky performance status (≥80 vs <80), IMDC risk group (intermediate vs poor risk; by definition, favorable-risk patients were not included), clear cell versus non–clear cell histology, sarcomatoid dedifferentiation, number of metastatic sites (continuous), and location of metastases (lung, brain, liver, bone, and lymph node). In order to account for immortal time bias, deferred cytoreductive nephrectomy was operationalized as a time-varying covariate
Additional comments	Arm level baseline characteristics were not reported in the study

Study arms

Upfront cytoreductive nephrectomy + sunitinib (N = 805)

Sunitinib + deferred cytoreductive nephrectomy (N = 85)

Sunitinib alone (N = 651)

Characteristics

Study-level characteristics

Characteristic	Study (N = 1541)
% Female No of events	n = 403 ; % = 26
Age Median (IQR)	61 (54 to 68)
Primary RCC type - Clear cell histology No of events	n = 1311 ; % = 85
Primary RCC type - Sarcomatoid dedifferentiation No of events	n = 232 ; % = 15
Location of metastases - Brain No of events	n = 130 ; % = 8
Location of metastases - lung No of events	n = 1141 ; % = 74
Location of metastases - Liver No of events	n = 333 ; % = 22
Location of metastases - bone No of events	n = 593 ; % = 38
Location of metastases - Nodal No of events	n = 785 ; % = 51
Location of metastases - Other sites No of events	n = 461 ; % = 30

Characteristic	Study (N = 1541)
IMDC risk - Poor IMDC risk No of events	n = 618 ; % = 40
Number of metastatic sites - One No of events	n = 435 ; % = 28
Number of metastatic sites - Two No of events	n = 546 ; % = 35
Number of metastatic sites - Three No of events	n = 371 ; % = 24
Number of metastatic sites - Four No of events	n = 147 ; % = 10
Number of metastatic sites - Five + No of events	n = 42 ; % = 3

Outcomes

Survival

Outcome	Upfront cytoreductive nephrectomy + sunitinib vs Sunitinib alone, , N2 = 651, N1 = 805	Sunitinib + deferred cytoreductive nephrectomy vs Upfront cytoreductive nephrectomy + sunitinib, , N2 = 805, N1 = 85
Overall survival Hazard ratio/95% CI	0.6 (0.53 to 0.68)	0.52 (0.39 to 0.7)

Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest)*
Directness	Directly applicable

Chakiryan, 2022

Bibliographic Reference	Chakiryan, Nicholas H; Gore, L Robert; Reich, Richard R; Dunn, Rodney L; Jiang, Da David; Gillis, Kyle A; Green, Elizabeth; Hajiran, Ali; Hugar, Lee; Zemp, Logan; Zhang, Jingsong; Jain, Rohit K; Chahoud, Jad; Spiess, Philippe E; Manley, Brandon J; Sexton, Wade J; Hollenbeck, Brent K; Gilbert, Scott M; Survival Outcomes Associated With Cytoreductive Nephrectomy in Patients With Metastatic Clear Cell Renal Cell Carcinoma.; JAMA network open; 2022; vol. 5 (no. 5); e2212347

Study details

Study type	Retrospective cohort study
Study location	United States - Uses the National Clinical Data Base (NCDB)
Study dates	January 2006 to December 2016
Sources of funding	NR
Inclusion criteria	Clinical stage IV metastatic renal cancer at diagnosis; age of 18 to 100 years; availability of complete staging and demographic data; and receipt of targeted therapy as first-line treatment Diagnosis with clear cell renal cell carcinoma
Exclusion criteria	NCDB codes indicated that the patient was treated on an experimental or blinded clinical trial protocol; data were missing on distance from the patient's residence to the treating facility; if The International Metastatic Renal Cell Carcinoma Database risk score were not available in the NCDB, and available data points are not adequate to calculate this score directly
Intervention(s)	Up-front cytoreductive nephrectomy (CN)
Comparator	First line systemic anti-cancer therapy only i.e. no cytoreductive nephrectomy
Outcome measures	Overall survival
Number of participants	Overall - 12,154 Up-front cytoreductive nephrectomy= 4,393 Systemic anti-cancer therapy alone - 7,761
Duration of follow-up	Median follow-up time for patients who were alive at last contact was 36.0 months (IQR, 22.3-56.7 months)
Loss to follow-up	Not reported
Methods of analysis	Patients were stratified according to the cytoreductive nephrectomy status. Wilcoxon rank sum testing was used to compare continuous variables, and the χ2 test of independence was used to compare categorical variables.

	Kaplan-Meier estimates were used to generate survival functions. Propensity score matching carried out. Univariable analysis was repeated in the post-matching cohorts to assess for balance between groups. Subgroup analysis was conducted for each of the 3 methods (multivariable Cox proportional hazards regression, propensity score matching, and instrumental variable analysis) to test whether the cytoreductive nephrectomy sequence with targeted therapy administration was associated with overall survival Adjusted covariates: age, sex, race, Charlson-Deyo score, facility type, year of diagnosis, cT stage, cN stage, and cytoreductive nephrectomy status
Additional comments	Study included 12, 766 participants in total with 5,005 in the cytoreductive nephrectomy arm and 7,761 in no cytoreductive nephrectomy arm. The protocol relevant outcomes were extracted from the subset of the cytoreductive nephrectomy arm who received up-front cytoreductive nephrectomy compared to no cytoreductive nephrectomy arm (4,393 vs. 7,761). However, the baseline data was not reported for this subset but as an overall for the participants who had received cytoreductive nephrectomy and was extracted (5,005 and 7,761). Study uses and reports the protocol relevant outcomes based on both multiple-cox regression and propensity score matching model. The extracted results came from the propensity score matching model.

Study arms

Cytoreductive nephrectomy (N = 5005)

Upfront nephrectomy + SACT - N= 4393

SACT Alone (N = 7761)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy (N = 5005)	SACT Alone (N = 7761)
% Female No of events	n = 1540 ; % = 31	n = 2482 ; % = 32
Age Median (IQR)	61 (54 to 67)	65 (57 to 72)

Characteristic	Cytoreductive nephrectomy (N = 5005)	SACT Alone (N = 7761)
TNM classification - cT1 No of events	n = 887 ; % = 18	n = 2295 ; % = 30
TNM classification - cT2 No of events	n = 1721 ; % = 34	n = 2213 ; % = 29
TNM classification - cT3 No of events	n = 2049 ; % = 41	n = 2101 ; % = 27
TNM classification - cT4 No of events	n = 348 ; % = 7	n = 1152 ; % = 15
TNM classification - cN0 No of events	n = 3579 ; % = 72	n = 4366 ; % = 56
TNM classification - cN+ No of events	n = 1426 ; % = 28	n = 3395 ; % = 44

Outcomes

Survival

Outcome	Cytoreductive nephrectomy vs SACT Alone, , N2 = 4393, N1 = 7761
Overall survival Upfront Hazard ratio/95% CI	0.5 (0.48 to 0.52)

Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Insufficient adjustment for confounders, limited reporting on missing data and protocol not identified)*
Directness	Directly applicable

Choueiri, 2011

Bibliographic Reference	Choueiri, Toni K; Xie, Wanling; Kollmannsberger, Christian; North, Scott; Knox, Jennifer J; Lampard, J Geoffrey; McDermott, David F; Rini, Brian I; Heng, Daniel Y C; The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy.; The Journal of urology; 2011; vol. 185 (no. 1); 60-6

Study details

Study type	Retrospective cohort study
Study location	US and Canada
Study dates	August 2004 and July 2008
Inclusion criteria	Patients diagnosis of metastatic renal cell carcinoma of any pathological subtype Patients treated with sunitinib, sorafenib or bevacizumab
Exclusion criteria	Patients who had undergone nephrectomy for early stage disease and metastases had subsequently developed
Intervention(s)	Cytoreductive nephrectomy, before systemic anti-cancer therapy
Comparator	No cytoreductive nephrectomy, only systemic anti-cancer therapy
Number of participants	N = 314 Cytoreductive nephrectomy N=201 No cytoreductive nephrectomy N = 113
Duration of follow-up	Median followup after treatment initiation in those alive was 16.3 months
Loss to follow-up	Not reported
Methods of analysis	Distributions of overall survival were estimated using the Kaplan-Meier method and medians with 95% confidence intervals were reported. Proportional hazards regression was used to examine the association between cytoreductive nephrectomy and overall survival when adjusted for the Heng et al. or Memorial Sloan-Kettering Cancer Centre criteria. Survival curves were constructed for each of the Heng et al, and Memorial Sloan-Kettering Cancer Centre favorable, intermediate and poor risk groups, and hazard ratio and Wald chi-square test from Cox regression were performed. This was also performed in different subgroups including patients with or without brain metastases, those with Karnofsky performance status 80% or greater vs less than 80%, those with more than 1 site of metastasis vs 1 site of metastasis, and those on different types of vascular endothelial growth factor targeted therapy

Study arms

Cytoreductive nephrectomy, before systemic anti-cancer therapy (N = 201)

No cytoreductive nephrectomy, only systemic anti-cancer therapy (N = 113)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy, before systemic anti-cancer therapy (N = 201)	No cytoreductive nephrectomy, only systemic anti-cancer therapy (N = 113)
% Female No of events	n = 62 ; % = 30.8	n = 30 ; % = 26.5
Number of metastatic sites - One No of events	n = 45 ; % = 22.4	n = 37 ; % = 32.7
Number of metastatic sites - More than 1 No of events	n = 156 ; % = 77.6	n = 76 ; % = 67.3
Brain metastases - No No of events	n = 180 ; % = 89.6	n = 105 ; % = 92.9
Brain metastases - Yes No of events	n = 21 ; % = 10.4	n = 8 ; % = 7.1
Nonclear cell pathology - No No of events	n = 180 ; % = 91.4	n = 89 ; % = 96.7
Nonclear cell pathology - Yes No of events	n = 17 ; % = 8.6	n = 3 ; % = 3.3
Sarcomatoid features - No No of events	n = 182 ; % = 92.4	n = 85 ; % = 94.4
Sarcomatoid features - Yes No of events	n = 15 ; % = 7.6	n = 5 ; % = 5.6

Characteristic	Cytoreductive nephrectomy, before systemic anti-cancer therapy (N = 201)	No cytoreductive nephrectomy, only systemic anti-cancer therapy (N = 113)
Type of therapy - Sunitinib No of events	n = 114 ; % = 56.7	n = 84 ; % = 74.3
Type of therapy - Sorafenib No of events	n = 72 ; % = 35.8	n = 22 ; % = 19.5
Type of therapy - Bevacizumab No of events	n = 15 ; % = 7.5	n = 7 ; % = 6.2
Diagnosis to targeted therapy less than 1 yr - No No of events	n = 63 ; % = 31.3	n = 9 ; % = 8
Diagnosis to targeted therapy less than 1 yr - Yes No of events	n = 138 ; % = 68.7	n = 104 ; % = 92
Hemoglobin less than lower level normal - No No of events	n = 68 ; % = 35.6	n = 34 ; % = 32.1
Hemoglobin less than lower level normal - Yes No of events	n = 123 ; % = 64.4	n = 72 ; % = 67.9
Serum corrected calcium greater than upper limit normal - No No of events	n = 178 ; % = 93.7	n = 76 ; % = 74.5
Serum corrected calcium greater than upper limit normal - Yes No of events	n = 12 ; % = 6.3	n = 26 ; % = 25.5

Characteristic	Cytoreductive nephrectomy, before systemic anti-cancer therapy (N = 201)	No cytoreductive nephrectomy, only systemic anti-cancer therapy (N = 113)
LDH greater than 1.5 upper limit normal - No No of events	n = 144 ; % = 85.7	n = 73 ; % = 83
LDH greater than 1.5 upper limit normal - Yes No of events	n = 24 ; % = 14.3	n = 15 ; % = 17
Neutrophils greater than upper limit normal - No No of events	n = 159 ; % = 87.9	n = 77 ; % = 79.4
Neutrophils greater than upper limit normal - Yes No of events	n = 22 ; % = 12.1	n = 20 ; % = 20.6
Platelets greater than upper limit normal - No No of events	n = 141 ; % = 74.6	n = 71 ; % = 68.3
Platelets greater than upper limit normal - Yes No of events	n = 48 ; % = 25.4	n = 33 ; % = 31.7

Outcomes

Survival

Outcome	Cytoreductive nephrectomy, before systemic anti-cancer therapy vs No cytoreductive nephrectomy, only systemic anti-cancer therapy, , N2 = 113, N1 = 201
OS Hazard ratio/95% CI	0.68 (0.46 to 0.99)

OS - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest)*
Directness	Directly applicable

de Groot, 2016

Bibliographic Reference	de Groot, Saskia; Redekop, William K; Sleijfer, Stefan; Oosterwijk, Egbert; Bex, Axel; Kiemeney, Lambertus A L M; Uyl-de Groot, Carin A; Survival in Patients With Primary Metastatic Renal Cell Carcinoma Treated With Sunitinib With or Without Previous Cytoreductive Nephrectomy: Results From a Population-based Registry.; Urology; 2016; vol. 95; 121-7

Study details

Trial registration number and/or trial name	PERCEPTION-registry
Study type	Retrospective cohort study
Study location	Netherlands - Patients registried from the Dutch Cancer Registry
Study dates	January 2008 and December 2010
Sources of funding	The PERCEPTION-registry was supported by grants from the Netherlands Organisation for Health Research and Development (grant number 152001014), Pfizer (formerly Wyeth Pharmaceuticals BV), and Roche Nederland BV. From the Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands; the Department of Medical Oncology and Cancer Genomics Netherlands, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; the Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Department of Urology, Nijmegen, The Netherlands; the Department of Urology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; and the Radboud Institute for Health Sciences, Radboud University Medical Center, Department for Health Evidence, Nijmegen, The Netherlands
Inclusion criteria	Patients treated with first-line sunitinib Patients diagnosed with metastatic renal cell carcinoma (ie, metastases at initial presentation) of any histologic subtype
Intervention(s)	Cytoreductive nephrectomy + sunitinib

Comparator	Sunitinib only
Outcome measures	Overall survival
Number of participants	N = 146 Cytoreductive nephrectomy + sunitinib N=73 Sunitinib only N=73
Methods of analysis	Overall survival was calculated from the date of the start of treatment (i.e., cytoreductive nephrectomy or start of first-line sunitinib) until the date of death from any cause or last follow-up using the Kaplan-Meier method. The first approach to evaluate the effect of cytoreductive nephrectomy was a Cox proportional hazards model using the propensity score as a covariate. Baseline demographics (age at diagnosis and gender) and 3 additional clinical factors (histology, clinical tumour stage, and regional lymph node involvement) were incorporated as covariates because these factors could have influenced the decision to conduct a nephrectomy

Study arms

Cytoreductive nephrectomy + sunitinib (N = 73)

Sunitinib only (N = 73)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy + sunitinib (N = 73)	Sunitinib only (N = 73)
% Female No of events	n = 60 ; % = 82	n = 60 ; % = 83
Age Median (IQR)	62 (28 to 77)	64 (24 to 89)
TNM classification - cT1-T3a No of events	n = 60 ; % = 82	n = 59 ; % = 81

Characteristic	Cytoreductive nephrectomy + sunitinib (N = 73)	Sunitinib only (N = 73)
TNM classification - cT3b-T4 No of events	n = 13 ; % = 18	n = 14 ; % = 19
TNM classification - cN0 No of events	n = 37 ; % = 50	n = 32 ; % = 44
TNM classification - cN1 No of events	n = 36 ; % = 50	n = 41 ; % = 56
Primary RCC type - Clear cell No of events	n = 57 ; % = 78	n = 57 ; % = 78
Primary RCC type - other No of events	n = 16 ; % = 22	n = 16 ; % = 22
Site of metastasis - One No of events	n = 33 ; % = 45	n = 39 ; % = 54
Site of metastasis - More than one No of events	n = 40 ; % = 55	n = 34 ; % = 46
Liver metastasis - No No of events	n = 67 ; % = 92	n = 68 ; % = 94
Liver metastasis - Yes No of events	n = 6 ; % = 8	n = 5 ; % = 6
Lung metastasis - No No of events	n = 16 ; % = 22	n = 24 ; % = 32
Lung metastasis - Yes No of events	n = 57 ; % = 78	n = 49 ; % = 68
Bone metastasis - No No of events	n = 58 ; % = 79	n = 61 ; % = 84
Bone metastasis - Yes	n = 15 ; % = 21	n = 12 ; % = 16

Characteristic	Cytoreductive nephrectomy + sunitinib (N = 73)	Sunitinib only (N = 73)
No of events		

Outcomes

Survival

Outcome	Cytoreductive nephrectomy + sunitinib vs Sunitinib only, , N2 = 73, N1 = 73
Overall survival - Cytoreductive nephrectomy Hazard ratio/95% CI	0.61 (0.41 to 0.92)

Overall survival - Cytoreductive nephrectomy - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest)*
Directness	Directly applicable

Dragomir, 2022

Bibliographic Reference	Dragomir, A.; Nazha, S.; Tanguay, S.; Breau, R.H.; Bhindi, B.; Rendon, R.A.; Kapoor, A.; Hotte, S.J.; Basappa, N.; Fairey, A.; So, A.I.; Kollmannsberger, C.; Finelli, A.; Hansen, A.; Canil, C.; Heng, D.; Lattouf, J.-B.; Bjarnason, G.; Power, N.; Pouliot, F.; Wood, L.A.; Outcomes of Cytoreductive Nephrectomy for Patients with Metastatic Renal Cell Carcinoma: Real World Data from Canadian Centers; European Urology Focus; 2022; vol. 8 (no. 6); 1703-1710

Study details

Study type	Retrospective cohort study
Study location	Canada - Data retrieved from the Canadian Kidney Cancer information system (CKCis)
Study dates	January 2011 and April 2020
Sources of funding	The Kidney Cancer Research Network of Canada and the Canadian Kidney Cancer information system (CKCis) have received unrestricted

	grants from BMS, Eisai, EMD Serono, GSK, Ipsen, Pfizer, Merck, Novartis, and Roche. These sponsors had no direct role in or influence on this work
Inclusion criteria	Diagnosis of renal cell carcinoma was made on the basis of histopathological evaluations; patients with synchronous disease (i.e., metastases found 3 months before or within 6 months after the primary tumour diagnosis); treated (with cytoreductive nephrectomy or/and systemic therapy) within 12 months of the initial renal cell carcinoma diagnosis
Exclusion criteria	Patients who had indolent metastatic disease
Intervention(s)	Cytoreductive nephrectomy followed by systemic therapy (cytoreductive nephrectomy before systemic therapy)
Comparator	Systemic therapy followed by cytoreductive nephrectomy (cytoreductive nephrectomy after systemic therapy) and systemic therapy alone (systemic therapy only)
Outcome measures	Overall survival
Number of participants	N = 708 Cytoreductive nephrectomy before systemic therapy - N = 383 Cytoreductive nephrectomy after systemic therapy - N = 73 Systemic therapy only - N = 252
Duration of follow-up	Earliest date of death, loss to follow-up, or the end of the study period (April 2020)
Loss to follow-up	Not reported
Methods of analysis	Kaplan Meier curve analysis was performed to estimate overall survival from the index date until death (any causes) or loss to follow-up. A log-rank test was used to evaluate differences in overall survival. Uses Inverse probability of treatment weighting to account for the differences in the distribution among baseline characteristics. It uses the inverse probability of treatment weighting and Cox proportional hazard model to adjust only for age, gender, sites and number of organs with metastasis, histology, International Metastatic Consortium (IMDC) scores and Charlson comorbidity index.

Study arms

Cytoreductive nephrectomy before systemic therapy (N = 383)

Cytoreductive nephrectomy after systemic therapy (N = 73)

Systemic therapy only (N = 252)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy before systemic therapy (N = 383)	Cytoreductive nephrectomy after systemic therapy (N = 73)	Systemic therapy only (N = 252)
% Female No of events	n = 104 ; % = 27.1	n = 19 ; % = 26	n = 128 ; % = 50.8
Age Median (IQR)	61 (54 to 68)	62 (55 to 68)	64 (57 to 70)
Primary RCC type - Clear cell histology No of events	n = 314 ; % = 82	n = 61 ; % = 83.6	n = 169 ; % = 67.1
Location of metastases - lung No of events	n = 215 ; % = 56.1	n = 39 ; % = 53.4	n = 135 ; % = 53.6
Location of metastases - bone No of events	n = 75 ; % = 19.6	n = 14 ; % = 19.2	n = 66 ; % = 26.2
Location of metastases - Brain No of events	n = 7 ; % = 1.8	n = 2 ; % = 2.7	n = 16 ; % = 6.4
Location of metastases - Adrenal gland No of events	n = 41 ; % = 10.7	n = 10 ; % = 13.7	n = 29 ; % = 11.5
Location of metastases - Liver No of events	n = 36 ; % = 9.4	n = 9 ; % = 12.3	n = 41 ; % = 16.3

Characteristic	Cytoreductive nephrectomy before systemic therapy (N = 383)	Cytoreductive nephrectomy after systemic therapy (N = 73)	Systemic therapy only (N = 252)
Location of metastases - Lymph nodes No of events	n = 122 ; % = 31.9	n = 28 ; % = 38.4	n = 104 ; % = 41.3
Systemic therapy type - Sunitinib No of events	n = 230 ; % = 60.1	n = 52 ; % = 71.2	n = 121 ; % = 48
Systemic therapy type - Pazopanib No of events	n = 72 ; % = 18.8	n = 8 ; % = 11	n = 52 ; % = 20.6
Systemic therapy type - Ipilimumab/nivolumab No of events	n = 44 ; % = 11.5	n = 3 ; % = 4.1	n = 57 ; % = 22.6
Systemic therapy type - Other No of events	n = 37 ; % = 9.6	n = 10 ; % = 13.7	n = 22 ; % = 8.8
IMDC Score - 0 (good) No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
IMDC Score - 1–2 (intermediate) No of events	n = 253 ; % = 66.1	n = 48 ; % = 65.8	n = 133 ; % = 52.8
IMDC Score - 3-5 (poor) No of events	n = 130 ; % = 33.9	n = 25 ; % = 34.2	n = 119 ; % = 47.2
Charlson comorbidity index - 0 or 1 No of events	n = 95 ; % = 27	n = 20 ; % = 28.6	n = 55 ; % = 23.8
Charlson comorbidity index - >1 No of events	n = 257 ; % = 73	n = 50 ; % = 71.4	n = 175 ; % = 76.2

Characteristic	Cytoreductive nephrectomy before systemic therapy (N = 383)	Cytoreductive nephrectomy after systemic therapy (N = 73)	Systemic therapy only (N = 252)
Comorbidities - Hypertension No of events	n = 204 ; % = 53.3	n = 28 ; % = 38.4	n = 121 ; % = 48
Comorbidities - Diabetes No of events	n = 83 ; % = 21.7	n = 16 ; % = 21.9	n = 57 ; % = 22.6
Comorbidities - Obesity No of events	n = 12 ; % = 3.1	n = 2 ; % = 2.7	n = 11 ; % = 4.4
Comorbidities - Hypercholesterolemia No of events	n = 89 ; % = 23.2	n = 11 ; % = 15.1	n = 47 ; % = 18.7
Comorbidities - Smoker No of events	n = 8 ; % = 2.1	n = 3 ; % = 4.1	n = 2 ; % = 0.8

Outcomes

Survival

Outcome	Cytoreductive nephrectomy before systemic therapy vs Systemic therapy only, , N2 = 252, N1 = 383	Cytoreductive nephrectomy after systemic therapy vs Cytoreductive nephrectomy before systemic therapy, , N2 = 383, N1 = 73
Overall survival Hazard ratio/95% CI	0.65 (0.52 to 0.82)	0.66 (0.42 to 1.04)

Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(No adjustment for confounders or matching undertaken. Limited information about missing data or inclusion criteria. No protocol*

Question	Answer
	identified so unable to fully assess bias in selection of reported result.)
Directness	Directly applicable

Ghatalia, 2022

Bibliographic Reference	Ghatalia, Pooja; Handorf, Elizabeth A; Geynisman, Daniel M; Deng, Mengying; Zibelman, Matthew R; Abbosh, Philip; Anari, Fern; Greenberg, Richard E; Viterbo, Rosalia; Chen, David; Smaldone, Marc C; Kutikov, Alexander; Uzzo, Robert G; The Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma: A Real-World Multi-Institutional Analysis.; The Journal of urology; 2022; vol. 208 (no. 1); 71-79

Study details

Study type	Retrospective cohort study
Study location	US - uses the nationwide US Flatiron Health (FH) electronic health record (EHR)-derived deidentified database.
Study dates	2011-2020
Sources of funding	This work was not supported by external funding
Inclusion criteria	Patients with clear cell histology and synchronous metastases
Intervention(s)	Upfront cytoreductive nephrectomy
Comparator	Deferred cytoreductive nephrectomy Systemic therapy alone
Outcome measures	Overall survival
Number of participants	N = 1,719 Upfront cytoreductive nephrectomy - N = 605 Deferred cytoreductive nephrectomy - N = 142 Systemic therapy alone - N = 972
Duration of follow-up	Not reported
Loss to follow-up	Not reported

Methods of analysis	Kaplan-Meier curves, log-rank tests, and Cox proportional hazards regressions were used to assess the effect of therapy on survival. Adjusted analyses were conducted via Inverse Probability of Treatment Weighing (IPTW) based on the generalized propensity score, with propensity scores estimated via Bayesian Additive Regression Trees. Covariates in the propensity score model were age, gender, race, insurance at diagnosis, and IMDC risk group. Where covariates were missing, we used a missing category in the propensity score model. Propensity scores were assessed for overlap, and weighted observations were assessed for covariate balance, with a standardized difference of <0.1 taken to indicate sufficient balance. Weighted Kaplan-Meier curves and Cox models were then used.

Study arms

Upfront cytoreductive nephrectomy (N = 605)

Deferred cytoreductive nephrectomy (N = 142)

Systemic therapy alone (N = 972)

Characteristics

Arm-level characteristics

Characteristic	Upfront cytoreductive nephrectomy (N = 605)	Deferred cytoreductive nephrectomy (N = 142)	Systemic therapy alone (N = 972)
% Female No of events	n = 187 ; % = 31	n = 41 ; % = 29	n = 297 ; % = 31
Age Median (IQR)	62.3 (56 to 69)	63.2 (58 to 70)	67 (60 to 75)
Baseline performance status - ECOG 0 No of events	n = 160 ; % = 26	n = 37 ; % = 26	n = 213 ; % = 22
Baseline performance status - ECOG 1 No of events	n = 144 ; % = 24	n = 29 ; % = 20	n = 264 ; % = 27
Baseline performance status - ECOG 2 No of events	n = 36 ; % = 6	n = 11 ; % = 8	n = 116 ; % = 12

Characteristic	Upfront cytoreductive nephrectomy (N = 605)	Deferred cytoreductive nephrectomy (N = 142)	Systemic therapy alone (N = 972)
Baseline performance status - ECOG 3 No of events	n = 7 ; % = 1	*empty data*	n = 32
Baseline performance status - ECOG 4 No of events	*empty data*	*empty data*	n = 3 ; % = 0.3
Baseline performance status - Missing No of events	n = 258 ; % = 43	n = 59 ; % = 42	n = 344 ; % = 35
Race - white No of events	n = 438 ; % = 72	n = 101 ; % = 71	n = 670 ; % = 70
Race - Black No of events	n = 23 ; % = 4	n = 8 ; % = 6	n = 55 ; % = 6
Race - Hispanic No of events	n = 6 ; % = 1	n = 0 ; % = 0	n = 2 ; % = 0.2
Race - Asian No of events	n = 10 ; % = 2	n = 2 ; % = 2	n = 13 ; % = 2
Race - Other No of events	n = 84 ; % = 14	n = 21 ; % = 15	n = 130 ; % = 13
Race - Missing No of events	n = 44 ; % = 7	n = 10 ; % = 7	n = 102 ; % = 11
IMDC risk category - Intermediate No of events	n = 90 ; % = 15	n = 29 ; % = 20	n = 149 ; % = 15
IMDC risk category - Poor No of events	n = 211 ; % = 35	n = 47 ; % = 33	n = 443 ; % = 46

Characteristic	Upfront cytoreductive nephrectomy (N = 605)	Deferred cytoreductive nephrectomy (N = 142)	Systemic therapy alone (N = 972)
IMDC risk category - Poor/Intermediate No of events	n = 304 ; % = 50	n = 66 ; % = 47	n = 380 ; % = 39

Outcomes

Survival

Outcome	Upfront cytoreductive nephrectomy vs Systemic therapy alone, , N2 = 972, N1 = 605	Upfront cytoreductive nephrectomy vs Deferred cytoreductive nephrectomy, , N2 = 142, N1 = 605
Overall survival Hazard ratio/95% CI	0.83 (0.7 to 0.96)	1 (0.76 to 1.32)

Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Insufficient adjustment for confounders, limited reporting on missing data and protocol not identified)*
Directness	Directly applicable

Gunenc, 2024

Bibliographic Reference	Gunenc, Damla; Issa, Wadih; Gerald, Thomas; Zhou, Qinhan; Zhang, Song; Ibezue, I Chidera; Bhanvadia, Raj; Tachibana, Isamu; Brugarolas, James; Hammers, Hans; Qin, Qian; Kapur, Payal; Woldu, Solomon; Gaston, Kris; Lotan, Yair; Cadeddu, Jeffrey; Wang, Andrew Z; Margulis, Vitaly; Zhang, Tian; Pathological Response and Outcomes in Patients With Metastatic Renal Cell Carcinoma (mRCC) Receiving Immunotherapy-Based Therapies and Undergoing Deferred Cytoreductive Nephrectomy (CN).; Clinical genitourinary cancer; 2024; vol. 22 (no. 5); 102177

Study details

Study type	Retrospective cohort study
Study location	US
Study dates	April 2016 - October 2022
Sources of funding	Bristol-Myers Squibb, Merck & Co, Ararvive, Surface oncology, NGM Biopharmaceutical, CPRIT, Janssen, Astra Zeneca, Pfizer, Astellas, Eli Lilly, Tempus, ALX Oncology, Janux Therapeutics, Exelixis, FBD Biologics, Guardant, OncoC4
Inclusion criteria	Patients with metastatic RCC receiving immunotherapy-based therapies and undergoing deferred or upfront CN
Exclusion criteria	Patients who did not receive immunotherapy based therapies
Intervention(s)	Upfront CN - patients who were started on immunotherapy inhibitor-based therapies after surgery
Comparator	Deferred CN - patients who were receiving immunotherapy-based therapies before surgery
Outcome measures	Progression-free survival Overall survival
Number of participants	N=51
Duration of follow-up	Median follow-up of 21 months
Loss to follow-up	No additional information
Methods of analysis	Kaplan Meier analysis was performed for Progression Free Survival (PFS) and Overall Survival (OS) estimates over time. Estimated Blood Loss (EBL) were evaluated using the Mann-Whitney-U test.
Additional comments	The baseline timepoint was defined as the initiation of immune checkpoint inhibitor therapies for the deferred CN group and the time of nephrectomy for the upfront CN group. Categorical variables between the two groups were compared using the Chi-square test.

Study arms

Upfront CN (N = 13)

Upfront cytoreductive nephrectomy group included those who were receiving immunotherapy based therapies after surgery

Deferred CN (N = 38)

Deferred cytoreductive nephrectomy group included those who were receiving immunotherapy based therapies in the preoperative setting

Characteristics

Arm-level characteristics

Characteristic	Upfront CN (N = 13)	Deferred CN (N = 38)
% Female No of events	n = 3 ; % = 13	n = 9 ; % = 23.7
Age (years) Mean (SD)	59.62 (NR)	62.53 (NR)
TNM classification - T1 stage No of events	n = 1 ; % = 7.7	n = 2 ; % = 5.3
TNM classification - T2 stage No of events	n = 0 ; % = 0	n = 6 ; % = 15.8
TNM classification - T3 stage No of events	n = 9 ; % = 69.2	n = 19 ; % = 50
TNM classification - T4 stage No of events	n = 3 ; % = 23.1	n = 11 ; % = 28.9
TNM classification - N0 stage No of events	n = 5 ; % = 38.5	n = 23 ; % = 60.5
TNM classification - N1 stage No of events	n = 7 ; % = 53.8	n = 13 ; % = 39.5

Characteristic	Upfront CN (N = 13)	Deferred CN (N = 38)
Primary RCC type - clear cell No of events	n = 10 ; % = 76.9	n = 34 ; % = 89.5
Primary RCC type - Papillary No of events	n = 2 ; % = 15.4	n = 1 ; % = 2.6
Primary RCC type - Other No of events	n = 1 ; % = 7.7	n = 3 ; % = 7.9
Location of metastases - Bone, brain, or liver metastases No of events	n = 4 ; % = 30.8	n = 19 ; % = 50

Outcomes

Progression free survival

Outcome	Upfront CN vs Deferred CN, , N2 = 38, N1 = 13
Progression free survival Hazard ratio/95% CI	0.7 (0.29 to 1.98)
Overall survival Hazard ratio/95% CI	0.4 (0.13 to 1.57)

Critical appraisal - ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Retrospective study design so difficult to account for confounders and not clear if there was selection bias in the selection of patients for upfront or deferred CN. There was no mention of adjusting for selection biases. The systemic therapies varied. Different follow-up durations but only median follow-up reported.)*
Directness	Directly applicable

Hara, 2023

Bibliographic Reference	Hara, Takuto; Furukawa, Junya; Shiraishi, Yusuke; Okamura, Yasuyoshi; Bando, Yukari; Terakawa, Tomoaki; Harada, Kenichi; Nakano, Yuzo;

Fujisawa, Masato; Impact of cytoreductive nephrectomy prior to combination therapy of ipilimumab plus nivolumab in metastatic renal cell carcinoma.; International journal of urology : official journal of the Japanese Urological Association; 2023; vol. 30 (no. 9); 746-752

Study details

Study type	Retrospective cohort study
Study location	Japan - used the institutional medical record database at Kobe University Hospital and five affiliated hospitals
Study dates	October 2018 and December 2021
Sources of funding	Not reported
Inclusion criteria	Patients who received nivolumab plus ipilimumab for synchronous metastatic renal cell carcinoma
Exclusion criteria	Patients who received deferred cytoreductive nephrectomy
Intervention(s)	Cytoreductive nephrectomy before ipilimumab plus nivolumab
Comparator	Without cytoreductive nephrectomy
Outcome measures	Progression-free survival Overall survival
Number of participants	N = 54 Cytoreductive nephrectomy prior to ipilimumab plus nivolumab - N = 21 Without cytoreductive nephrectomy - N = 33
Duration of follow-up	Median follow-up was 15.7 months
Loss to follow-up	Not reported
Methods of analysis	The progression-free survival and overall survival rates were calculated by the Kaplan–Meier method, and differences were analyzed by the log-rank test. progression-free survival and overall survival of the patients treated with either prior cytoreductive nephrectomy or not were compared after propensity score matching of patient cohorts to reduce potential confounding effects and treatment selection bias. The covariates were age, body mass index (BMI), sex, International Metastatic RCC Database Consortium (IMDC) risk classification, histology, presence of liver, brain, or bone metastasis, clinical T stage, neutrophil lymphocyte ratio (NLR), PS, number of metastasis and presence of tumour

	associated symptoms (e.g., pain, paralysis, fever, weight loss). Nearest-neighbor matching with a 1:1 ratio and a caliper distance of 0.2 was used.

Study arms

Cytoreductive nephrectomy before ipilimumab plus nivolumab (N = 21)

Without cytoreductive nephrectomy (N = 33)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy before ipilimumab plus nivolumab (N = 21)	Without cytoreductive nephrectomy (N = 33)
% Female No of events	n = 2 ; % = 15.4	n = 2 ; % = 15.4
Age Median (IQR)	71 (42 to 80)	71 (30 to 81)
Primary RCC type - Clear cell No of events	n = 10 ; % = 76.9	n = 8 ; % = 61.5
Primary RCC type - Non–clear cell No of events	n = 3 ; % = 23.1	n = 5 ; % = 38.5
IMDC risk - Intermediate No of events	n = 6 ; % = 46.2	n = 6 ; % = 46.2
IMDC risk - Poor No of events	n = 7 ; % = 53.8	n = 7 ; % = 53.8

Outcomes

Survival

Outcome	Cytoreductive nephrectomy before ipilimumab plus nivolumab vs Without cytoreductive nephrectomy, , N2 = 33, N1 = 21
Progression-free survival	0.41 (0.18 to 0.91)

Outcome	Cytoreductive nephrectomy before ipilimumab plus nivolumab vs Without cytoreductive nephrectomy, , N2 = 33, N1 = 21
Hazard ratio/95% CI	
Overall survival Hazard ratio/95% CI	0.21 (0.06746 to 0.63)

Progression-free survival - Polarity - Higher values are better
Overall survival - Polarity - Higher values are better

Adverse events ≥ grade 3

Outcome	Cytoreductive nephrectomy before ipilimumab plus nivolumab, , N = 21	Without cytoreductive nephrectomy, , N = 33
Adverse events ≥ grade 3 No of events	n = 10 ; % = 47.6	n = 9 ; % = 27.3

Adverse events ≥ grade 3 - Polarity - Lower values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest.)*
Directness	Directly applicable

Hatakeyama, 2021

Bibliographic Reference	Hatakeyama, Shingo; Naito, Sei; Numakura, Kazuyuki; Kato, Renpei; Koguchi, Tomoyuki; Kojima, Takahiro; Kawasaki, Yoshihide; Kandori, Shuya; Kawamura, Sadafumi; Tsushima, Eiki; Nishiyama, Hiroyuki; Ito, Akihiro; Kojima, Yoshiyuki; Habuchi, Tomonori; Obara, Wataru; Tsuchiya, Norihiko; Ohyama, Chikara; Impact of cytoreductive nephrectomy in patients with primary metastatic renal cell carcinoma receiving systemic tyrosine kinase inhibitor therapy: A multicenter retrospective study.; International journal of urology : official journal of the Japanese Urological Association; 2021; vol. 28 (no. 4); 369-375

Study details

Study type	Retrospective cohort study
Study location	Japan - Michinoku Japan Urological Cancer Study Group database

Study dates	January 2008 - November 2019
Sources of funding	Japan Society for the Promotion of Science
Inclusion criteria	Patients with primary metastatic renal cell carcinoma initially treated with first-line sunitinib, sorafenib, axitinib, and pazopanib were included
Exclusion criteria	Treatment with first-line interferon, mammalian target of rapamycin inhibitors, immunotherapy, or chemotherapy; a period from diagnosis to first treatment (tyrosine kinase inhibitors or immediate cytoreductive nephrectomy) of more than 3 months; a period of surveillance after immediate cytoreductive nephrectomyof more than 3 months; a follow-up period from the first treatment of less than 3 months; and missing data on confounder variables
Intervention(s)	Immediate cytoreductive nephrectomy followed by first-line tyrosine kinase inhibitors
Comparator	Deferred cytoreductive nephrectomy - after receiving tyrosine kinase inhibitors Systemic anti-cancer therapy alone - tyrosine kinase inhibitors
Outcome measures	Overall survival
Number of participants	N = 278 Immediate cytoreductive nephrectomy followed by first-line tyrosine kinase inhibitors - N = 107 Deferred cytoreductive nephrectomy - after receiving tyrosine kinase inhibitors - N = 39 Systemic anti-cancer therapy alone - tyrosine kinase inhibitors - N = 132
Duration of follow-up	Until death
Loss to follow-up	Not reported
Methods of analysis	Overall survival from the initial treatment until death was estimated using Kaplan–Meier curves and the log-rank test. Uses inverse probability of treatment weighting (inverse probability of treatment weighting) -adjusted Cox regression analysis. Adjusted confounders - age, sex, performance status, number of IMDC risk factors, clinical stage (cT3b–4), and number of metastatic organs

Study arms

Immediate cytoreductive nephrectomy (N = 107)

Deferred cytoreductive nephrectomy (N = 39)

Systemic anti-cancer therapy alone (N = 132)

Characteristics

Arm-level characteristics

Characteristic	Immediate cytoreductive nephrectomy (N = 107)	Deferred cytoreductive nephrectomy (N = 39)	Systemic anti-cancer therapy alone (N = 132)
% Female No of events	n = 28 ; % = 26.2	n = 17 ; % = 43.6	n = 32 ; % = 24.2
Age Median (IQR)	62 (56 to 69)	67 (62 to 72)	67 (61 to 76)
Intervention subtype - Sunitinib No of events	n = 72 ; % = 67	n = 17 ; % = 44	n = 65 ; % = 49
Intervention subtype - Sorafenib No of events	n = 10 ; % = 9.3	n = 2 ; % = 5.2	n = 16 ; % = 12
Intervention subtype - Axitinib No of events	n = 15 ; % = 14	n = 19 ; % = 49	n = 47 ; % = 36
Intervention subtype - Pazopanib No of events	n = 10 ; % = 9.3	n = 1 ; % = 2.6	n = 4 ; % = 3
TNM classification - cT1–2 No of events	n = 37 ; % = 35	n = 14 ; % = 36	n = 32 ; % = 24
TNM classification - cT3a No of events	n = 47 ; % = 44	n = 8 ; % = 21	n = 34 ; % = 26

Characteristic	Immediate cytoreductive nephrectomy (N = 107)	Deferred cytoreductive nephrectomy (N = 39)	Systemic anti-cancer therapy alone (N = 132)
TNM classification - cT3b–4 No of events	n = 19 ; % = 18	n = 17 ; % = 44	n = 63 ; % = 48
TNM classification - cTx (unknown) No of events	n = 4 ; % = 4	n = 0 ; % = 0	n = 3 ; % = 2
TNM classification - cN+ No of events	n = 40 ; % = 37	n = 11 ; % = 28	n = 65 ; % = 49
Primary RCC type - Non–clear cell No of events	n = 12 ; % = 11	n = 3 ; % = 7.7	n = 21 ; % = 16
Location of metastases - lung No of events	n = 74 ; % = 69	n = 23 ; % = 59	n = 77 ; % = 58
Location of metastases - Distant lymph node No of events	n = 40 ; % = 37	n = 11 ; % = 28	n = 49 ; % = 37
Location of metastases - bone No of events	n = 38 ; % = 36	n = 14 ; % = 36	n = 38 ; % = 29
Location of metastases - Liver No of events	n = 11 ; % = 10	n = 3 ; % = 8	n = 23 ; % = 17
Location of metastases - Adrenal No of events	n = 11 ; % = 10	n = 1 ; % = 3	n = 16 ; % = 12
Location of metastases - Brain No of events	n = 11 ; % = 10	n = 2 ; % = 5	n = 9 ; % = 7

Characteristic	Immediate cytoreductive nephrectomy (N = 107)	Deferred cytoreductive nephrectomy (N = 39)	Systemic anti-cancer therapy alone (N = 132)
Location of metastases - Pancreas No of events	n = 5 ; % = 5	n = 0 ; % = 0	n = 5 ; % = 4
Location of metastases - Others No of events	n = 23 ; % = 21	n = 8 ; % = 21	n = 46 ; % = 35

Outcomes

Survival

Outcome	Immediate cytoreductive nephrectomy vs Systemic anti-cancer therapy alone, , N2 = 132, N1 = 107	Deferred cytoreductive nephrectomy vs Immediate cytoreductive nephrectomy, , N2 = 39, N1 = 107
Overall survival Hazard ratio/95% CI	0.63 (0.42 to 0.93)	0.61 (0.32 to 1.14)

Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest)*
Directness	Directly applicable

Macleod, 2018

Bibliographic Reference	Macleod, Liam C; Odisho, Anobel Y; Tykodi, Scott S; Holt, Sarah K; Harper, Jonathan D; Gore, John L; Comparative Effectiveness of Initial Surgery vs Initial Systemic Therapy for Metastatic Kidney Cancer in the Targeted Therapy Era: Analysis of a Population-based Cohort.; Urology; 2018; vol. 113; 146-152

Study details

Study type	Retrospective cohort study
Study location	US - data use agreement set forth by The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program data linked with Medicare claims
Study dates	2006 - 2011
Sources of funding	This work was funded in part by a seed grant from the AMA Foundation
Inclusion criteria	Patients with continuous Medicare fee-for-service coverage
Exclusion criteria	Incomplete treatment claims data Under 66 years of age Patients receiving cytoreductive nephrectomy but no additional therapy Competing non-metastatic renal cell carcinoma stage IV cancer
Intervention(s)	Initial cytoreductive nephrectomy
Comparator	Initial systemic therapy
Outcome measures	Overall survival
Number of participants	N = 537 Initial cytoreductive nephrectomy N=190 Initial systemic therapy N=347
Duration of follow-up	Median follow-up 12 months (IQR 5.2, 22 months)
Loss to follow-up	Not reported
Methods of analysis	Kaplan-Meier estimates the overall survival, stratified by treatment, and compared mortality with the log-rank test. Propensity for initial cytoreductive nephrectomy was calculated based on age, gender, race, marital status, urban or rural status, histologic subtype, clinical T and N classification, comorbidity index, and grade. A propensity score adjusted model was performed using Cox proportional hazards regression. Covariates were selected a priori based on proven impact on overall survival and included demographic factors (age, race, ethnicity, rural status), treatment era (first half and latter half of study period), cancer severity (tumor stage, nodal status, histology), comorbidity (Charlson-Klabunde index), and SEER registry

Study arms

Initial cytoreductive nephrectomy (N = 190)

Initial systemic therapy (N = 347)

Characteristics

Arm-level characteristics

Characteristic	Initial cytoreductive nephrectomy (N = 190)	Initial systemic therapy (N = 347)
% Female No of events	n = 68 ; % = 35.8	n = 163 ; % = 47
TNM classification - 1-2 No of events	n = 84 ; % = 44.2	n = 196 ; % = 56.5
TNM classification - 3-4 No of events	n = 103 ; % = 54.2	n = 88 ; % = 25.4
TNM classification - missing No of events	n = 3 ; % = 1.6	n = 63 ; % = 18.1
Primary RCC type - Clear cell No of events	n = 56 ; % = 29.5	n = 215 ; % = 62
Primary RCC type - Other RCC No of events	n = 134 ; % = 70.5	n = 132 ; % = 38
Race - white No of events	n = 165 ; % = 86.8	n = 289 ; % = 83.3
Race - Non white No of events	n = 25 ; % = 13.2	n = 58 ; % = 16.7
Grade - 1-2 No of events	n = 45 ; % = 23.7	n = 38 ; % = 11
Grade - 3-4	n = 115 ; % = 60.5	n = 40 ; % = 11.5

Characteristic	Initial cytoreductive nephrectomy (N = 190)	Initial systemic therapy (N = 347)
No of events		
Grade - Missing No of events	n = 30 ; % = 15.8	n = 269 ; % = 77.5

Outcomes

Survival

Outcome	Initial cytoreductive nephrectomy vs Initial systemic therapy, , N2 = 347, N1 = 190
Overall survival Hazard ratio/95% CI	1.94 (1.49 to 2.53)

Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Insufficient adjustment for confounders,)*
Directness	Directly applicable

Manley, 2017

Bibliographic Reference	Manley, Brandon J; Kim, Eric H; Vetter, Joel M; Potretzke, Aaron M; Strope, Seth A; Validation of preoperative variables and stratification of patients to help predict benefit of cytoreductive nephrectomy in the targeted therapy ERA.; International braz j urol : official journal of the Brazilian Society of Urology; 2017; vol. 43 (no. 3); 432-439

Study details

Study type	Retrospective cohort study
Study location	United States
Study dates	2005 - 2013
Sources of funding	Not reported
Inclusion criteria	Patients with metastatic renal cell carcinoma who received systemic targeted therapy

Exclusion criteria	Patients with missing survival data Patients with incomplete clinical data Patients who received prior immunotherapy
Intervention(s)	Cytoreductive nephrectomy + targeted therapy
Comparator	Targeted therapy alone
Outcome measures	Overall survival
Number of participants	N = 123 Cytoreductive nephrectomy + targeted therapy N=88 Targeted therapy alone N=35
Duration of follow-up	Not reported
Loss to follow-up	Not reported
Methods of analysis	Kaplan-Meier estimated overall survival was compared between cytoreductive nephrectomy and targeted therapy groups. Log rank p-values were calculated to compare survival curves. Multivariate cox proportional hazards analysis was also performed adjusting for age and comorbidity

Study arms

Cytoreductive nephrectomy + targeted therapy (N = 88)

Targeted therapy alone (N = 35)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy + targeted therapy (N = 88)	Targeted therapy alone (N = 35)
Age Mean (SD)	57.4 (10.4)	57.8 (10.4)
TNM classification No of events	n = 36 ; % = 41	n = 13 ; % = 37

Characteristic	Cytoreductive nephrectomy + targeted therapy (N = 88)	Targeted therapy alone (N = 35)
Location of metastases - Liver No of events	n = 18 ; % = 20	n = 11 ; % = 31

Outcomes

Survival

Outcome	Cytoreductive nephrectomy + targeted therapy vs Targeted therapy alone, , N2 = 35, N1 = 88
Overall survival Hazard ratio/95% CI	0.39 (0.23 to 0.65)

Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest)*
Directness	Directly applicable

Meagher, 2024

Bibliographic Reference	Meagher, Margaret F; Minervini, Andrea; Mir, Maria C; Cerrato, Clara; Rebez, Giacomo; Autorino, Riccardo; Hampton, Lance; Campi, Riccardo; Kriegmair, Maximilian; Linares, Estefania; Hevia, Vital; Musquera, Maria; D'Anna, Mauricio; Roussel, Eduard; Albersen, Maarten; Pavan, Nicola; Claps, Francesco; Antonelli, Alessandro; Marchioni, Michele; Paksoy, Nail; Erdem, Selcuk; Derweesh, Ithaar H; Does the Timing of Cytoreductive Nephrectomy Impact Outcomes? Analysis of REMARCC Registry Data for Patients Receiving Tyrosine Kinase Inhibitor Versus Immune Checkpoint Inhibitor Therapy.; European urology open science; 2024; vol. 63; 71-80

Study details

Study type	Retrospective cohort study
Study location	Italy Spain
Study dates	January 2006 - October 2019

Sources of funding	Stephen Weissman Kidney Cancer Research Fund. The funding body played a role in management and analysis of the data.
Inclusion criteria	Patients with metastatic RCC receiving tyrosine kinase inhibitor or immunotherapy as systemic treatment and undergoing deferred or upfront CN
Exclusion criteria	Exclusion criteria not reported
Intervention(s)	Upfront cytoreductive nephrectomy (CN) CN prior to first line systemic therapy with tyrosine kinase inhibitor or immunotherapy.
Comparator	Deferred cytoreductive nephrectomy (CN) CN following first line systemic therapy with tyrosine kinase inhibitor or immunotherapy.
Outcome measures	Overall survival Mortality reported Cancer-specific survival Cancer specific mortality reported
Number of participants	N=189
Duration of follow-up	23.2 months median follow-up
Loss to follow-up	None
Methods of analysis	Multivariable proportional-hazards regression analysis was conducted for ACM and CSM. The Kaplan-Meier method was used to analyse median OS and CSS, with stratification by type of systemic therapy and the timing of CN.
Additional comments	International multi-institutional analysis using Registry of Metastatic RCC (REMARCC) data for patients presenting with metastatic RCC (mRCC) between January 2006 and October 2019 who underwent CN. Patients received either TKI or ICI first-line therapy. The type of systemic therapy provided and the treatment protocol were chosen at an institutional level. The type of surgery, CN timing, and surgical approach were at the surgeon’s discretion.

Study arms

Upfront CN (N = 141)

Systemic therapy with tyrosine kinase inhibitor or immunotherapy following cytoreductive nephrectomy

Deferred CN (N = 48)

Cytoreductive nephrectomy following systemic therapy with tyrosine kinase inhibitor or immunotherapy

Characteristics

Study-level characteristics

Characteristic	Study (N = 189)
% Female No of events	n = 44 ; % = 23
Age (years) Mean (SD)	62.13 (11.07)
TNM classification - cT1 No of events	n = 27 ; % = 14.3
TNM classification - cT2 No of events	n = 50 ; % = 26.5
TNM classification - cT3 No of events	n = 90 ; % = 47.6
TNM classification - cT4 No of events	n = 21 ; % = 11.1
TNM classification - N0 No of events	n = 107 ; % = 56.6
TNM classification - N1 No of events	n = 79 ; % = 41.8
TNM classification - NX	n = 3 ; % = 1.6

Characteristic	Study (N = 189)
No of events	

Outcomes

Mortality

Outcome	Upfront CN vs Deferred CN, , N2 = 48, N1 = 141
All-cause mortality Hazard ratio/95% CI	1.49 (1.02 to 2.17)
Cancer-specific mortality Hazard ratio/95% CI	2.04 (1.35 to 3.13)

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Retrospective study using data from registry. It isn't clear how participants were selected. Potential confounding due to different therapeutic approaches and follow-up protocols. The systemic agents varied according to centre.)*
Directness	Directly applicable

Patel, 2016

Bibliographic Reference	Patel, Nishant; Woo, Jason; Liss, Michael A; Palazzi, Kerrin L; Randall, J Michael; Mehrazin, Reza; Jabaj, Ramzi; Mirheydar, Hossein S; Gillis, Kyle; Lee, Hak J; Patterson, Anthony L; Kane, Christopher J; Millard, Frederick; Derweesh, Ithaar H; Does timing of targeted therapy for metastatic renal cell carcinoma impact treatment toxicity and surgical complications? A comparison of primary and adjuvant approaches.; The Canadian journal of urology; 2016; vol. 23 (no. 2); 8227-33

Study details

Study type	Retrospective cohort study
Study location	United States
Study dates	July 2007 to January 2014
Sources of funding	Not reported
Inclusion criteria	Primary systemic therapy was offered to all patients

	Patients diagnosed with metastatic renal cell carcinoma
Exclusion criteria	Patients with overwhelming burden of metastatic disease, with poor performance status, who proceeded to systemic therapy after the initial evaluation without a plan to offer cytoreductive nephrectomy Patients who undergone prior chemotherapy or immunotherapy Patients in whom the primary targeted treatment was other than sunitinib Patients were also excluded if tumour histology was not clear cell renal cell carcinoma Patients with < 3 months follow-up with no clear evidence of death or progression within that period
Intervention(s)	Cytoreductive nephrectomy + sunitinib
Comparator	Sunitinib + cytoreductive nephrectomy
Outcome measures	Severe adverse events
Number of participants	N = 48 Cytoreductive nephrectomy + sunitinib N=27 Sunitinib + cytoreductive nephrectomy N=21
Duration of follow-up	Median follow-up from first treatment (IQR), months: Cytoreductive nephrectomy + sunitinib = 28.1 (11.8-36.9) Sunitinib + cytoreductive nephrectomy = 42.5 (8.7-61.0)
Loss to follow-up	Not reported
Methods of analysis	Tests performed included the independent t-test, analysis of variance, MannWhitney U test, and Kruskal-Wallace tests for continuous variables (dependent on distribution), and Chi-square and Fisher exact tests for categorical values.

	Variables entered into the model included treatment group, age, race, BMI, ECOG, type of procedure performed, surgical approach, RENAL nephrometry score, tumour grade, and presence of thrombus.

Study arms

Cytoreductive nephrectomy + sunitinib (N = 27)

Sunitinib + cytoreductive nephrectomy (N = 21)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy + sunitinib (N = 27)	Sunitinib + cytoreductive nephrectomy (N = 21)
% Female No of events	n = 10 ; % = 37	n = 7 ; % = 33.3
Age Mean (SD)	59 (14.9)	57 (12.5)
Race - Caucasian No of events	n = 19 ; % = 70.4	n = 8 ; % = 40
Race - Other No of events	n = 8 ; % = 29.6	n = 12 ; % = 60
ECOG performance status - 0-1 No of events	n = 19 ; % = 70.4	n = 19 ; % = 90.5
ECOG performance status - >1 No of events	n = 8 ; % = 29.6	n = 2 ; % = 9.5
Number of metastases - 1-5 No of events	n = 13 ; % = 61.9	n = 15 ; % = 88.2
Number of metastases - >5 No of events	n = 8 ; % = 38.1	n = 2 ; % = 11.8

Outcomes

Duration of hospital stay

Outcome	Cytoreductive nephrectomy + sunitinib, , N = 27	Sunitinib + cytoreductive nephrectomy, , N = 21
Duration of hospital stay Median (IQR)	4.5 (3 to 8)	7 (5 to 11)
Surgical complications - High grade 3a/b (Clavien-Dindo) No of events	n = 0 ; % = 0	n = 6 ; % = 26.8

Duration of hospital stay - Polarity - Lower values are better
Surgical complications - High grade 3a/b (Clavien-Dindo) - Polarity - Lower values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest. No protocol identified so unable to fully assess bias in selection of reported result.)*
Directness	Directly applicable

Poprach, 2020

Bibliographic Reference	Poprach, Alexandr; Holanek, Milos; Chloupkova, Renata; Lakomy, Radek; Stanik, Michal; Fiala, Ondrej; Melichar, Bohuslav; Kopeckova, Katerina; Zemanova, Milada; Kiss, Igor; Penka, Igor; Bohosova, Julia; Buchler, Tomas; Cytoreductive Nephrectomy and Overall Survival of Patients with Metastatic Renal Cell Carcinoma Treated with Targeted Therapy-Data from the National Renis Registry.; Cancers; 2020; vol. 12 (no. 10)

Study details

Study type	Retrospective cohort study
Study location	Czech Republic - RenIS Registry database
Study dates	2007 to 2018
Sources of funding	This work was supported in part by the Ministry of Health, Czech Republic—Conceptual Development of Research Organization (MMCI 00209805) and supported by grant NV18-03-00554 and NV19-08-00250 from the Ministry of Health of Czech Republic. The RenIS registry is funded

	in part by pharmaceutical companies producing targeted agents for renal cancer (Pfizer, Bayer, Glaxo Smith Kline, Roche, and Novartis).
Inclusion criteria	Patients with synchronous metastatic disease subsequently treated with first-line targeted therapies with pazopanib or sunitinib Patients having cytoreductive nephrectomy within 3 months from the metastatic renal cell carcinoma diagnosis and subsequently treated with targeted therapies
Intervention(s)	Cytoreductive nephrectomy + targeted therapies
Comparator	Targeted therapies
Outcome measures	Progression-free survival Overall survival
Number of participants	N = 730 Cytoreductive nephrectomy + targeted therapies N=458 Targeted therapies N=272
Duration of follow-up	Not reported
Loss to follow-up	Not reported
Methods of analysis	Progression-free survival and overall survival were estimated using the Kaplan–Meier method, and all point estimates include 95% confidence intervals (95% CI). Statistical significance of differences in survival among subgroups was assessed using the log-rank test. Multivariable Cox proportional hazards models were used to evaluate the effect of all potential prognostic factors on the survival measures

Study arms

Cytoreductive nephrectomy + targeted therapies (N = 458)

Targeted therapies (N = 272)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy + targeted therapies (N = 458)	Targeted therapies (N = 272)
% Female No of events	n = 120 ; % = 26.2	n = 72 ; % = 26.5

Characteristic	Cytoreductive nephrectomy + targeted therapies (N = 458)	Targeted therapies (N = 272)
Age Median (IQR)	62 (25 to 83)	64 (35 to 85)
Intervention subtype - Sunitinib No of events	n = 361 ; % = 78.8	n = 210 ; % = 72.2
Intervention subtype - Pazopanib No of events	n = 97 ; % = 21.2	n = 62 ; % = 22.8
Primary RCC type - Clear cell carcinoma No of events	n = 431 ; % = 94.1	n = 261 ; % = 96
Primary RCC type - Papillary cell carcinoma No of events	n = 22 ; % = 4.8	n = 8 ; % = 2.9
Primary RCC type - Chromophobe cell carcinoma No of events	n = 2 ; % = 0.4	n = 2 ; % = 0.7
Primary RCC type - Bellini duct carcinoma No of events	n = 2 ; % = 0.4	n = 0 ; % = 0
Primary RCC type - unknown No of events	n = 1 ; % = 0.2	n = 1 ; % = 0.4
MSKCC score - Good No of events	n = 3 ; % = 0.7	n = 7 ; % = 2.6
MSKCC score - Intermediate No of events	n = 417 ; % = 91	n = 215 ; % = 79
MSKCC score - Poor No of events	n = 38 ; % = 8.3	n = 50 ; % = 18.4
ECog - < 2	n = 433 ; % = 94.5	n = 258 ; % = 94.9

Characteristic	Cytoreductive nephrectomy + targeted therapies (N = 458)	Targeted therapies (N = 272)
No of events		
ECog - ≥ 2 No of events	n = 25 ; % = 5.5	n = 14 ; % = 5.1

Outcomes

Survival

Outcome	Cytoreductive nephrectomy + targeted therapies vs Targeted therapies, , N2 = 272, N1 = 458
Progression-free survival Hazard ratio/95% CI	0.63 (0.53 to 0.76)
Overall survival Hazard ratio/95% CI	0.55 (0.45 to 0.68)

Progression-free survival - Polarity - Higher values are better
Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest. No protocol identified so unable to fully assess bias in selection of reported result.)*
Directness	Directly applicable

Singla, 2020

Bibliographic Reference	Singla, Nirmish; Hutchinson, Ryan C; Ghandour, Rashed A; Freifeld, Yuval; Fang, Dong; Sagalowsky, Arthur I; Lotan, Yair; Bagrodia, Aditya; Margulis, Vitaly; Hammers, Hans J; Woldu, Solomon L; Improved survival after cytoreductive nephrectomy for metastatic renal cell carcinoma in the contemporary immunotherapy era: An analysis of the National Cancer Database.; Urologic oncology; 2020; vol. 38 (no. 6); 604e9-604e17

Study details

Study type	Retrospective cohort study
Study location	US - uses the National Cancer Database (NCDB)
Study dates	2015 - 2016
Sources of funding	This work was supported, in part, by the Ruth L. Kirschstein National Research Service Award T32 CA136515-09 (N.S.), the University of Texas Southwestern Medical Center Physician Scientist Training Program (N.S.), and Dedman Family Scholarship in Clinical Care (A.B.).
Inclusion criteria	Patients diagnosed with metastatic renal clear cell carcinoma Patients who received immunotherapy
Exclusion criteria	Patients who received any non-immunotherapy systemic therapies
Intervention(s)	Cytoreductive nephrectomy + immunotherapy
Comparator	Immunotherapy + cytoreductive nephrectomy
Outcome measures	Overall survival
Number of participants	N = 221 Cytoreductive nephrectomy + immunotherapy N=197 Immunotherapy + cytoreductive nephrectomy N=24
Duration of follow-up	Median follow-up of 14.7 months
Loss to follow-up	Not reported
Methods of analysis	Overall survival was compared between the two cohorts using Kaplan-Meier methods, and differences were analysed with the log-rank statistic. Clinicopathologic predictors for overall survival were assessed using multivariable Cox regression analyses. Missing data were excluded from comparative analyses. Variables of interest included patient demographics, performance of cytoreductive nephrectomy, presence of sarcomatoid features, primary tumour size, cT stage, cN stage, presence of bone, brain, liver, or lung metastases, number of known metastatic sites, and time to receipt of immunotherapy from diagnosis. Among patients who underwent

	cytoreductive nephrectomy, additional variables of interest included performance of lymph node dissection, Fuhrman grade, pT stage, pN stage, lymphovascular invasion, time to surgery from diagnosis, surgical margin status, inpatient length of stay for the operative admission, 30-day readmission rates following surgery, and timing of cytoreductive nephrectomy in relation to immunotherapy administration (immunotherapy administered before cytoreductive nephrectomy (delayed cytoreductive nephrectomy) versus upfront cytoreductive nephrectomy before immunotherapy)

Study arms

Cytoreductive nephrectomy + immunotherapy (N = 197)

Immunotherapy + cytoreductive nephrectomy (N = 24)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy + immunotherapy (N = 197)	Immunotherapy + cytoreductive nephrectomy (N = 24)
% Female No of events	n = 47 ; % = 23.9	n = 17 ; % = 29.2
Age Median (IQR)	56 (51 to 63)	65 (56 to 70)
TNM classification - cT1 No of events	n = 25 ; % = 12.7	n = 9 ; % = 37.5
TNM classification - cT2 No of events	n = 75 ; % = 38.1	n = 4 ; % = 16.7
TNM classification - cT3 No of events	n = 70 ; % = 35.5	n = 9 ; % = 37.5
TNM classification - cT4 No of events	n = 10 ; % = 5.1	n = 1 ; % = 4.2
TNM classification - cTx No of events	n = 17 ; % = 8.6	n = 1 ; % = 4.2

Characteristic	Cytoreductive nephrectomy + immunotherapy (N = 197)	Immunotherapy + cytoreductive nephrectomy (N = 24)
TNM classification - cN0 No of events	n = 130 ; % = 66	n = 18 ; % = 75
TNM classification - cN1 No of events	n = 49 ; % = 24.9	n = 5 ; % = 20.8
TNM classification - cNx No of events	n = 18 ; % = 9.1	n = 1 ; % = 4.2
Race - white No of events	n = 169 ; % = 85.8	n = 19 ; % = 79.2
Race - Black No of events	n = 7 ; % = 3.6	n = 3 ; % = 12.5
Race - Hispanic No of events	n = 13 ; % = 6.6	n = 2 ; % = 8.3
Race - Asian/Other No of events	n = 8 ; % = 4.1	n = 0 ; % = 0
Presence of bone metastases - Yes No of events	n = 56 ; % = 28.4	n = 17 ; % = 70.8
Presence of bone metastases - No No of events	n = 129 ; % = 65	n = 7 ; % = 29.2
Presence of bone metastases - Unknown No of events	n = 13 ; % = 6.6	n = 0 ; % = 0
Presence of brain metastases - Yes No of events	n = 14 ; % = 7.1	n = 0 ; % = 0
Presence of brain metastases - No No of events	n = 171 ; % = 86.8	n = 24 ; % = 100

Characteristic	Cytoreductive nephrectomy + immunotherapy (N = 197)	Immunotherapy + cytoreductive nephrectomy (N = 24)
Presence of brain metastases - Unknown No of events	n = 12 ; % = 6.1	n = 0 ; % = 0
Presence of liver metastases - Yes No of events	n = 15 ; % = 7.6	n = 2 ; % = 8.3
Presence of liver metastases - No No of events	n = 170 ; % = 86.3	n = 22 ; % = 91.7
Presence of liver metastases - Unknown No of events	n = 12 ; % = 6.1	n = 0 ; % = 0
Presence of lung metastases - Yes No of events	n = 135 ; % = 68.5	n = 12 ; % = 50
Presence of lung metastases - No No of events	n = 49 ; % = 24.9	n = 12 ; % = 50
Presence of lung metastases - Unknown No of events	n = 13 ; % = 6.6	n = 0 ; % = 0
Presence of bone, liver, or brain metastases - Yes No of events	n = 76 ; % = 38.6	n = 17 ; % = 70.8
Presence of bone, liver, or brain metastases - No No of events	n = 109 ; % = 55.3	n = 7 ; % = 29.2
Presence of bone, liver, or brain metastases - Unknown No of events	n = 12 ; % = 6.1	n = 0 ; % = 0

Outcomes

Survival

Outcome	Cytoreductive nephrectomy + immunotherapy vs Immunotherapy + cytoreductive nephrectomy, , N2 = 24, N1 = 197
Overall survival Hazard ratio/95% CI	0.25 (0.03 to 1.83)

Overall survival - Polarity - Higher values are better

Critical appraisal – ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Insufficient adjustment for confounders, missing data were excluded from comparative analyses, and limited reporting on missing data and protocol not identified)*
Directness	Directly applicable

Stroup, 2013

Bibliographic Reference	Stroup, Sean P; Raheem, Omer A; Palazzi, Kerrin L; Liss, Michael A; Mehrazin, Reza; Kopp, Ryan P; Patel, Nishant; Cohen, Seth A; Park, Samuel K; Patterson, Anthony L; Kane, Christopher J; Millard, Frederick; Derweesh, Ithaar H; Does timing of cytoreductive nephrectomy impact patient survival with metastatic renal cell carcinoma in the tyrosine kinase inhibitor era? A multi-institutional study.; Urology; 2013; vol. 81 (no. 4); 805-11

Study details

Study type	Retrospective cohort study
Study location	US - multi-institutional (University of California San Diego Medical Centre; San Diego Veterans Administration Medical Centre; University of Tennessee Health Sciences Centre Memphis)
Study dates	May 2005 to August 2009
Sources of funding	Not reported
Inclusion criteria	Patients diagnosed with metastatic renal cell carcinoma

Exclusion criteria	Patients with an overwhelming burden of metastatic disease, with poor performance status, who proceeded to systemic therapy after the initial evaluation without a plan to offer cytoreductive nephrectomy Patients who had undergone prior chemotherapy or immunotherapy Patients in whom the primary targeted treatment was other than sunitinib Patients with <3 months follow-up with no clear evidence of death or progression within that period Tumour histology was not clear cell renal cell carcinoma
Intervention(s)	Cytoreductive nephrectomy + sunitinib
Comparator	Sunitinib + cytoreductive nephrectomy Sunitinib alone
Outcome measures	Overall survival Cancer-specific survival
Number of participants	N = 35 Cytoreductive nephrectomy + sunitinib N=17 Sunitinib + cytoreductive nephrectomy N=11 Sunitinib alone N = 7
Duration of follow-up	Follow-up from first treatment, month Cytoreductive nephrectomy + sunitinib = 29.9 (IQR: 16.9-46.8) Sunitinib + cytoreductive nephrectomy = 32 (IQR: 24.5-70.8) Sunitinib alone = 4.6 (IQR: 3.5-7.5) Follow-up from surgery, month Cytoreductive nephrectomy + sunitinib = 29.9 (IQR: 16.9-46.8) Sunitinib + cytoreductive nephrectomy = 22.8 (IQR: 16.8-34.7)
Loss to follow-up	Not reported

Methods of analysis	Kaplan-Meier analysis was used to demonstrate unadjusted survival outcomes, and Cox regression was used to examine associations between survival outcomes and predictors of interest. The following variables were tried in the multivariate Cox regression models and removed if nonsignificant: age, race, BMI, ECOG score (0 or 1 vs >1), tumour size (<7 vs ≥7 cm), tumour grade, inferior vena cava thrombus, and number of metastatic lesions (<5 vs ≥5)

Study arms

Cytoreductive nephrectomy + sunitinib (N = 17)

Sunitinib + cytoreductive nephrectomy (N = 18)

Sunitinib alone (N = 7)

Sunitinib + cytoreductive nephrectomy (Outcome) (N = 11)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy + sunitinib (N = 17)	Sunitinib + cytoreductive nephrectomy (N = 18)	Sunitinib alone (N = 7)	Sunitinib + cytoreductive nephrectomy (Outcome) (N = 11)
% Female No of events	n = 7 ; % = 41.2	n = 10 ; % = 55.6	*empty data*	*empty data*
Age Mean (SE)	57 (17.2)	55 (9.9)	*empty data*	*empty data*
TNM classification - pT1 No of events	n = 0 ; % = 0	n = 4 ; % = 36.4	*empty data*	*empty data*
TNM classification - pT2 No of events	n = 2 ; % = 28.6	n = 4 ; % = 36.4	*empty data*	*empty data*
TNM classification - pT3 No of events	n = 4 ; % = 57.1	n = 2 ; % = 18.2	*empty data*	*empty data*

Characteristic	Cytoreductive nephrectomy + sunitinib (N = 17)	Sunitinib + cytoreductive nephrectomy (N = 18)	Sunitinib alone (N = 7)	Sunitinib + cytoreductive nephrectomy (Outcome) (N = 11)
TNM classification - pT4 No of events	n = 1 ; % = 14.3	n = 1 ; % = 9.1	*empty data*	*empty data*
Location of metastases - lung No of events	n = 13 ; % = 76.5	n = 11 ; % = 61.1	*empty data*	*empty data*
Location of metastases - Liver No of events	n = 5 ; % = 29.4	n = 7 ; % = 38.9	*empty data*	*empty data*
Location of metastases - Lymphadenopathy No of events	n = 5 ; % = 29.4	n = 5 ; % = 27.8	*empty data*	*empty data*
Location of metastases - Brain No of events	n = 1 ; % = 5.9	n = 2 ; % = 11.1	*empty data*	*empty data*
Location of metastases - bone No of events	n = 6 ; % = 35.3	n = 3 ; % = 16.7	*empty data*	*empty data*
Location of metastases - Adrenal No of events	n = 3 ; % = 17.6	n = 6 ; % = 33.3	*empty data*	*empty data*
Race - Caucasian No of events	n = 8 ; % = 72.7	n = 9 ; % = 50	*empty data*	*empty data*
Race - Other No of events	n = 3 ; % = 27.3	n = 9 ; % = 50	*empty data*	*empty data*
ECOG status - 0-1 No of events	n = 14 ; % = 82.4	n = 12 ; % = 66.7	*empty data*	*empty data*

Characteristic	Cytoreductive nephrectomy + sunitinib (N = 17)	Sunitinib + cytoreductive nephrectomy (N = 18)	Sunitinib alone (N = 7)	Sunitinib + cytoreductive nephrectomy (Outcome) (N = 11)
ECOG status - 2-3 No of events	n = 3 ; % = 17.6	n = 6 ; % = 33.3	*empty data*	*empty data*
Number of metastases - 1-5 No of events	n = 8 ; % = 53.3	n = 10 ; % = 58.8	*empty data*	*empty data*
Number of metastases - >5 No of events	n = 7 ; % = 46.7	n = 7 ; % = 41.2	*empty data*	*empty data*
Nephrectomy - Radical No of events	n = 17 ; % = 100	n = 5 ; % = 45.5	*empty data*	*empty data*
Nephrectomy - Partial No of events	n = 0 ; % = 0	n = 6 ; % = 54.4	*empty data*	*empty data*

Outcomes

Survival

Outcome	Cytoreductive nephrectomy + sunitinib vs Sunitinib + cytoreductive nephrectomy (Outcome), , N2 = 17, N1 = 11	Sunitinib alone vs Cytoreductive nephrectomy + sunitinib, , N2 = 7, N1 = 17
Cancer spacific survival Hazard ratio/95% CI	7.24 (0.93 to 56.63)	10.17 (2.39 to 43.3)
Overall death Hazard ratio/95% CI	7.95 (1.03 to 61.63)	8.38 (2.2 to 31.9)

Cancer spacific survival - Polarity - Higher values are better
Overall death - Polarity - Lower values are better

Critical appraisal – ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest and limited reporting on missing data and protocol not identified)*
Directness	Directly applicable

Takemura, 2023

Bibliographic Reference	Takemura, Kosuke; Ernst, Matthew S; Navani, Vishal; Wells, J Connor; Bakouny, Ziad; Donskov, Frede; Basappa, Naveen S; Wood, Lori A; Meza, Luis; Pal, Sumanta K; Szabados, Bernadett; Powles, Thomas; Beuselinck, Benoit; McKay, Rana R; Lee, Jae-Lyun; Ernst, D Scott; Kapoor, Anil; Yuasa, Takeshi; Choueiri, Toni K; Heng, Daniel Y C; Characterization of Patients with Metastatic Renal Cell Carcinoma Undergoing Deferred, Upfront, or No Cytoreductive Nephrectomy in the Era of Combination Immunotherapy: Results from the International Metastatic Renal Cell Carcinoma Database Consortium.; European urology oncology; 2023

Study details

Study type	Retrospective cohort study
Study location	Multicentre collaboration involving participants from more than 40 institutions worldwide: Australia, Belgium, Canada, Denmark, Germany, Greece, Italy, Japan, Mexico, Netherlands, New Zealand, Singapore, South Korea, Spain, UK, and the United States
Study dates	Not reported
Sources of funding	This study was supported by the Yasuda Medical Foundation (grant to Kosuke Takemura). The sponsor played no direct role in the study
Inclusion criteria	Patients received frontline immuno-oncology based combinations, including immuno-oncology/immuno-oncology doublet therapy (ie, nivolumab plus ipilimumab) and immuno-oncology/tyrosine kinase inhibitor combination therapy (ie, pembrolizumab plus axitinib, avelumab plus axitinib, nivolumab plus cabozantinib, or pembrolizumab plus lenvatinib) Patients diagnosed with either synchronous metastatic renal cell carcinoma or metachronous metastatic renal cell carcinoma without previous nephrectomy for localized renal cell carcinoma Patient did not die nor were censored within a fixed landmark time, with different landmark time periods (6, 9, 12, and 18 months) examined

Exclusion criteria	Patients with missing data for the date of diagnosis or metastasis Patients with missing data for whether they underwent nephrectomy, or the date of nephrectomy Patients with missing data for whether they are dead or alive, or the date of death or last follow-up
Intervention(s)	Deferred cytoreductive nephrectomy
Comparator	Upfront cytoreductive nephrectomy Immuno-oncology alone
Outcome measures	Overall survival
Number of participants	N = 807 Deferred cytoreductive nephrectomy N=40 Upfront cytoreductive nephrectomy N=327 Immuno-oncology alone N=440
Duration of follow-up	12 months
Loss to follow-up	Not reported
Methods of analysis	Kaplan-Meier curves were constructed, and the log-rank test was carried out to compare post-landmark overall survival curves by cytoreductive nephrectomy status. Cox proportional-hazards regression was used to assess overall survival hazard ratios by cytoreductive nephrectomy status, operationalised as a time-varying covariate to account for immortal time bias.

Study arms

Deferred cytoreductive nephrectomy (N = 40)

Upfront cytoreductive nephrectomy (N = 327)

Immuno-oncology alone (N = 440)

Characteristics

Arm-level characteristics

Characteristic	Deferred cytoreductive nephrectomy (N = 40)	Upfront cytoreductive nephrectomy (N = 327)	Immuno-oncology alone (N = 440)
% Female No of events	n = 6 ; % = 25	n = 45 ; % = 25	n = 52 ; % = 29
Age Median (IQR)	57 (50 to 65)	60 (52 to 67)	63 (57 to 70)
Primary RCC type - Non–clear cell No of events	n = 9 ; % = 45	n = 21 ; % = 14	n = 9 ; % = 7.6
Location of metastases - Brain No of events	n = 2 ; % = 8.7	n = 9 ; % = 5.2	n = 14 ; % = 8.1
Location of metastases - bone No of events	n = 6 ; % = 26	n = 41 ; % = 23	n = 77 ; % = 44
Location of metastases - Liver No of events	n = 1 ; % = 4.3	n = 23 ; % = 13	n = 32 ; % = 19
IMDC prognostic - Favorable No of events	n = 0 ; % = 0	n = 13 ; % = 7.7	n = 3 ; % = 2
IMDC prognostic - Intermediate No of events	n = 10 ; % = 53	n = 116 ; % = 69	n = 83 ; % = 54

Characteristic	Deferred cytoreductive nephrectomy (N = 40)	Upfront cytoreductive nephrectomy (N = 327)	Immuno-oncology alone (N = 440)
IMDC prognostic - Poor No of events	n = 9 ; % = 47	n = 39 ; % = 23	n = 67 ; % = 44

Outcomes

Mortality

Outcome	Deferred cytoreductive nephrectomy, , N = 40	Upfront cytoreductive nephrectomy, , N = 327	Immuno-oncology alone, , N = 440
Mortality No of events	n = 1 ; % = 2.5	n = 43 ; % = 13	n = 107 ; % = 24

Mortality - Polarity - Lower values are better

Critical appraisal – ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Insufficient adjustment for confounders and protocol not identified)*
Directness	Directly applicable

Xu, 2019

Bibliographic Reference	Xu, W.-H.; Wang, J.; Huo, D.-Z.; Yin, G.-C.; Cao, D.-L.; Shi, G.-H.; Qu, Y.-Y.; Ye, D.-W.; Zhang, H.-L.; C-reactive protein levels and survival following cytoreductive nephrectomy in 118 patients with metastatic renal cell carcinoma treated with sunitinib: A retrospective study; Medical Science Monitor; 2019; vol. 25; 8984-8994

Study details

Study type	Retrospective cohort study
Study location	China - Department of Urology, Fudan University Shanghai Cancer Centre (FUSCC) Shanghai,
Study dates	May 2009 and June 2018
Sources of funding	Not reported

Inclusion criteria	Patients who had metastases on initial diagnosis and who were treated by urologists according to the standard treatment at our institution
Intervention(s)	Cytoreductive nephrectomy+ sunitinib
Comparator	Sunitinib alone
Outcome measures	Progression-free survival Overall survival
Number of participants	N = 118 Cytoreductive nephrectomy+ sunitinib N=70 Sunitinib alone N=48
Duration of follow-up	Last day of follow-up (8th July 2018)
Loss to follow-up	Not reported
Methods of analysis	The follow-up duration was determined using the Kaplan-Meier method with 95% confidence intervals and assessed using a log-rank test.

Study arms

Cytoreductive nephrectomy+ sunitinib (N = 70)

Sunitinib alone (N = 48)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy+ sunitinib (N = 70)	Sunitinib alone (N = 48)
% Female No of events	n = 14 ; % = 34.3	n = 10 ; % = 20.8
TNM classification - T1 No of events	n = 0 ; % = 0	n = 2 ; % = 4.2
TNM classification - T2 No of events	n = 6 ; % = 8.6	n = 9 ; % = 18.8
TNM classification - T3	n = 35 ; % = 50	n = 27 ; % = 56.2

Characteristic	Cytoreductive nephrectomy+ sunitinib (N = 70)	Sunitinib alone (N = 48)
No of events		
TNM classification - T4 No of events	n = 29 ; % = 41.4	n = 10 ; % = 20.48
TNM classification - N0 No of events	n = 38 ; % = 54.3	n = 21 ; % = 43.8
TNM classification - N1 No of events	n = 32 ; % = 45.7	n = 27 ; % = 56.3
Primary RCC type - Clear cell No of events	n = 55 ; % = 78.6	n = 37 ; % = 77.1
Primary RCC type - Non–clear cell No of events	n = 15 ; % = 21.4	n = 11 ; % = 22.9
Location of metastases - lung No of events	n = 39 ; % = 55.7	n = 28 ; % = 58.3
Location of metastases - Bone No of events	n = 26 ; % = 37.1	n = 14 ; % = 29.2
Location of metastases - Liver No of events	n = 8 ; % = 11.4	n = 8 ; % = 16.7
Location of metastases - Brain No of events	n = 1 ; % = 1.4	n = 2 ; % = 4.2
Location of metastases - Pleural No of events	n = 3 ; % = 4.3	n = 2 ; % = 4.2
Location of metastases - Vena cava No of events	n = 2 ; % = 2.9	n = 8 ; % = 16.7
Location of metastases - Retroperitoneal No of events	n = 2 ; % = 2.9	n = 7 ; % = 14.6

Characteristic	Cytoreductive nephrectomy+ sunitinib (N = 70)	Sunitinib alone (N = 48)
Location of metastases - Other No of events	n = 12 ; % = 17.1	n = 10 ; % = 20.8
IMDC risk category - Intermediate-risk No of events	n = 36 ; % = 51.4	n = 20 ; % = 41.7
IMDC risk category - High-risk No of events	n = 34 ; % = 48.6	n = 27 ; % = 58.3

Outcomes

Survival

Outcome	Cytoreductive nephrectomy+ sunitinib vs Sunitinib alone, , N2 = 48, N1 = 70
Progression-free survival Hazard ratio/95% CI	1.13 (0.77 to 1.67)
Overall survival Hazard ratio/95% CI	0.96 (0.67 to 1.41)

Progression-free survival - Polarity - Higher values are better
Overall survival - Polarity - Higher values are better

Critical appraisal – ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest and limited reporting on missing data and protocol not identified)*
Directness	Directly applicable

Yoshino, 2022

Bibliographic Reference	Yoshino, Maki; Ishihara, Hiroki; Nemoto, Yuki; Nakamura, Kazutaka; Nishimura, Koichi; Tachibana, Hidekazu; Fukuda, Hironori; Toki, Daisuke; Yoshida, Kazuhiko; Kobayashi, Hirohito; Iizuka, Junpei; Shimmura, Hiroaki; Hashimoto, Yasunobu; Tanabe, Kazunari; Kondo, Tsunenori;

Takagi, Toshio; Therapeutic role of deferred cytoreductive nephrectomy in patients with metastatic renal cell carcinoma treated with nivolumab plus ipilimumab.; Japanese journal of clinical oncology; 2022; vol. 52 (no. 10); 1208-1214

Study details

Study type	Retrospective cohort study
Study location	Japan - five affiliated institutions (Tokyo Women's Medical University Hospital, Tokyo Women's Medical University Adachi Medical Centre, Saiseikai Kawaguchi General Hospital, Saiseikai Kurihashi Hospital and Tokiwakai Joban Hospital).
Study dates	September 2016 and July 2021
Sources of funding	Not reported
Inclusion criteria	Patients with synchronous metastatic renal cell carcinoma received nivolumab plus ipilimumab as first-line therapy
Exclusion criteria	Patients whose duration of post-treatment follow-up was short (i.e. <1 month) or whose clinical data were missing
Intervention(s)	Upfront cytoreductive nephrectomy + nivolumab plus ipilimumab initiation
Comparator	No cytoreductive nephrectomy Nivolumab plus ipilimumab + deferred cytoreductive nephrectomy
Outcome measures	Overall survival
Number of participants	N = 41 Upfront cytoreductive nephrectomy + nivolumab plus ipilimumab initiation N=21 No cytoreductive nephrectomy N=13 Nivolumab plus ipilimumab + deferred cytoreductive nephrectomy N=7
Duration of follow-up	Median of 12.0 months (interquartile range: 7.0–21.0 months)

Loss to follow-up	Not reported
Methods of analysis	Survival was calculated using the Kaplan–Meier method and compared using the log-rank test.

Study arms

Upfront cytoreductive nephrectomy + nivolumab plus ipilimumab initiation (N = 21)

No cytoreductive nephrectomy (N = 13)

Nivolumab plus ipilimumab + deferred cytoreductive nephrectomy (N = 7)

Characteristics

Arm-level characteristics

Characteristic	Upfront cytoreductive nephrectomy + nivolumab plus ipilimumab initiation (N = 21)	No cytoreductive nephrectomy (N = 13)	Nivolumab plus ipilimumab + deferred cytoreductive nephrectomy (N = 7)
% Female No of events	n = 8 ; % = 38.1	n = 5 ; % = 38.5	n = 1 ; % = 14.3
Age Median (IQR)	64 (53.5 to 69.5)	70 (56.5 to 69.5)	56 (47 to 64)
Primary RCC type - Clear-cell carcinoma No of events	n = 18 ; % = 85.7	n = 8 ; % = 61.5	n = 5 ; % = 71.4
Primary RCC type - Non-clear-cell carcinoma No of events	n = 3 ; % = 14.3	n = 2 ; % = 20	n = 1 ; % = 14.3
Primary RCC type - Papillary renal cell carcinoma No of events	n = 2 ; % = 9.52	n = 1 ; % = 7.7	n = 0 ; % = 0

Characteristic	Upfront cytoreductive nephrectomy + nivolumab plus ipilimumab initiation (N = 21)	No cytoreductive nephrectomy (N = 13)	Nivolumab plus ipilimumab + deferred cytoreductive nephrectomy (N = 7)
Primary RCC type - Others No of events	n = 1 ; % = 4.76	n = 1 ; % = 7.7	n = 1 ; % = 14.3
Primary RCC type - unknown No of events	n = 0 ; % = 0	n = 3 ; % = 23.1	n = 1 ; % = 14.3
Location of metastases - Liver No of events	n = 3 ; % = 14.3	n = 1 ; % = 7.7	n = 1 ; % = 14.3
Location of metastases - bone No of events	n = 7 ; % = 33.3	n = 0 ; % = 0	n = 1 ; % = 14.3
IMDC risk - Intermediate No of events	n = 14 ; % = 66.7	n = 4 ; % = 30.8	n = 1 ; % = 14.3
IMDC risk - Poor No of events	n = 7 ; % = 33.3	n = 9 ; % = 69.2	n = 5 ; % = 71.4
IMDC risk - Unknown No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 14.3

Outcomes

Survival

Outcome	Upfront cytoreductive nephrectomy + nivolumab plus ipilimumab initiation, , N = 21	No cytoreductive nephrectomy, , N = 13	Nivolumab plus ipilimumab + deferred cytoreductive nephrectomy, , N = 7
Overall survival - Nivolumab plus ipilimumab + deferred cytoreductive	n = 15 ; % = 72.4	*empty data*	n = 7 ; % = 100

Outcome	Upfront cytoreductive nephrectomy + nivolumab plus ipilimumab initiation, , N = 21	No cytoreductive nephrectomy, , N = 13	Nivolumab plus ipilimumab + deferred cytoreductive nephrectomy, , N = 7
nephrectomy vs. Upfront cytoreductive nephrectomy + nivolumab plus ipilimumab initiation No of events			
Overall survival - Nivolumab plus ipilimumab + deferred cytoreductive nephrectomy vs. No cytoreductive nephrectomy No of events	*empty data*	n = 8 ; % = 58.2	n = 7 ; % = 100

Overall survival - Polarity - Higher values are better

Critical appraisal – ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest)*
Directness	Directly applicable

You, 2011

Bibliographic Reference	You, Dalsan; Jeong, In Gab; Ahn, Jin-Hee; Lee, Dae Ho; Lee, Jae-Lyun; Hong, Jun Hyuk; Ahn, Hanjong; Kim, Choung-Soo; The value of cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy.; The Journal of urology; 2011; vol. 185 (no. 1); 54-9

Study details

Study type	Retrospective cohort study
Study location	Republic of Korea
Study dates	November 2006 to December 2009
Sources of funding	Not reported

Inclusion criteria	Patients diagnosed with metastatic renal clear cell carcinoma Patient with observable disease, and adequate haematological, coagulation, hepatic, renal and cardiopulmonary function
Exclusion criteria	Non-clear cell type renal cell carcinoma No evidence of residual disease due to complete nephrectomy and metastasectomy
Intervention(s)	Cytoreductive nephrectomy + targeted therapy
Comparator	Targeted therapy alone
Outcome measures	Progression-free survival Overall survival
Number of participants	N = 78 Cytoreductive nephrectomy + targeted therapy N=45 Targeted therapy alone N=33
Duration of follow-up	Not reported
Loss to follow-up	Not reported
Methods of analysis	Kaplan-Meier survival curves were used to estimate progression-free survival and overall survival, which were compared using the log-rank test. Cox proportional hazards model estimates the prognostic significance of each variable, including the Memorial Sloan-Kettering Cancer Centre prognostic factors
Additional comments	

Study arms

Cytoreductive nephrectomy + targeted therapy (N = 45)

Targeted therapy alone (N = 33)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy + targeted therapy (N = 45)	Targeted therapy alone (N = 33)
% Female No of events	n = 36 ; % = 80	n = 21 ; % = 64
Location of metastases - Brain No of events	n = 3 ; % = 7	n = 1 ; % = 3
Targeted agent - Sunitinib No of events	n = 34 ; % = 76	n = 29 ; % = 88
Targeted agent - Sorafenib No of events	n = 11 ; % = 24	n = 4 ; % = 12
Number metastatic sites - One No of events	n = 30 ; % = 67	n = 15 ; % = 45
Number metastatic sites - Greater than 1 No of events	n = 15 ; % = 33	n = 18 ; % = 55
Liver metastasis - No No of events	n = 43 ; % = 96	n = 28 ; % = 85
Liver metastasis - Yes No of events	n = 2 ; % = 4	n = 5 ; % = 15

Outcomes

Survival

Outcome	Cytoreductive nephrectomy + targeted therapy vs Targeted therapy alone, , N2 = 33, N1 = 45
Progression-free survival Hazard ratio/95% CI	1.5 (0.7 to 3.5)
Overall survival Hazard ratio/95% CI	1.9 (0.9 to 4.3)

Progression-free survival - Polarity - Higher values are better
Overall survival - Polarity - Higher values are better

Critical appraisal –ROBINS-I checklist

Question	Answer
Risk of bias judgement	Serious *(Analyses were not controlled for all confounding variables of interest)*
Directness	Directly applicable

Review 2 Systemic anti-cancer therapy then cytoreductive nephrectomy

Non-randomised controlled trials evidence

Bhindi, 2018

Bibliographic Reference	Bhindi, B.; Habermann, E.B.; Mason, R.J.; Costello, B.A.; Pagliaro, L.C.; Thompson, R.H.; Leibovich, B.C.; Boorjian, S.A.; Comparative Survival following Initial Cytoreductive Nephrectomy versus Initial Targeted Therapy for Metastatic Renal Cell Carcinoma; Journal of Urology; 2018; vol. 200 (no. 3); 528-534

Study details

Study type	Retrospective cohort study
Study location	United States - uses national clinical oncology (NCDB) database
Study dates	2006 - 2013
Sources of funding	Not reported
Inclusion criteria	Diagnosis with kidney cancer between 2006 and 2013 with being metastatic at the diagnosis
Exclusion criteria	another prior cancer history, non RCC or unknown histology, missing vital status or follow-up, a renal ablative procedure, inability to determine cytoreductive nephrectomy (CN) status, missing time to surgery in patients who underwent CN, missing time to targeted therapy (TT) in those who received TT and no treatment (CN or TT) within 3 months of diagnosis
Intervention(s)	Deferred cytoreductive nephrectomy - no information about the SACT
Comparator	SACT alone
Outcome measures	Overall survival
Number of participants	Deferred cytoreductive nephrectomy - 7526 SACT alone - not reported
Duration of follow-up	Until death
Methods of analysis	Cohort characteristics were compared between groups using the Wilcoxon rank sum test and the chi-square test. Factors associated with TT after initial CN and CN after initial TT were evaluated in separate multivariable Cox regression models. Overall survival was compared between the initial CN and initial TT groups using Kaplan-Meier analysis and Cox regression models with censoring at end of the study period or due to loss to follow-up. To account for differences in baseline characteristics which may have influenced the initial treatment selection authors used inverse probability of treatment weighting (IPTW) based on the propensity to receive initial CN vs

	initial TT, which was in turn estimated by logistic regression. Additional sensitivity analysis was also performed without assumptions to evaluate the potential impact of unmeasured confounders on the study conclusion.
Additional comments	The study does not report the number of participants in the SACT alone arm and baseline data for the protocol relevant comparison arm (deferred CN and SACT alone). Therefore, the baseline data extracted in EPPI is for the overall participants included in the study.

Study arms

Deferred cytoreductive nephrectomy (N = 7520)

SACT alone (N = NR)

Characteristics

Study-level characteristics

Characteristic	Study (N = 15068)
% Female Sample size	n = 4662 ; % = 30.9
Age - ≤50 Sample size	n = 2456 ; % = 16.3
Age - 51–60 Sample size	n = 4629 ; % = 30.7
Age - 61–70 Sample size	n = 4758 ; % = 31.6
Age - >70 Sample size	n = 3225 ; % = 21.4
TNM classification - cT1 Sample size	n = 2537 ; % = 16.8
TNM classification - cT2 Sample size	n = 3547 ; % = 23.5
TNM classification - cT3 Sample size	n = 4406 ; % = 29.2

Characteristic	Study (N = 15068)
TNM classification - cT4 Sample size	n = 1478 ; % = 9.8
TNM classification - cTx Sample size	n = 3100 ; % = 20.6
Primary RCC type - Clear cell Sample size	n = 6374 ; % = 42.3
Primary RCC type - Non-clear cell Sample size	n = 1417 ; % = 9.4
Primary RCC type - RCC- unknown subtype Sample size	n = 7227 ; % = 48.3

Outcomes

Overall survival

Outcome	Deferred cytoreductive nephrectomy vs SACT alone, , N2 = , N1 =
Overall survival Hazard ratio/95% CI	0.53 (0.46 to 0.6)

Overall survival - Polarity - Lower values are better

Critical appraisal - ROBIS checklist

Question	Answer
Risk of bias judgement	Serious *Insufficient adjustment for confounders, limited reporting on missing data and protocol not identified*
Directness	Directly applicable

Bhindi, 2020

Bibliographic Reference	Bhindi, Bimal; Graham, Jeffrey; Wells, J Connor; Bakouny, Ziad; Donskov, Frede; Fraccon, Anna; Pasini, Felice; Lee, Jae Lyun; Basappa, Naveen S; Hansen, Aaron; Kollmannsberger, Christian K; Kanesvaran, Ravindran; Yuasa, Takeshi; Ernst, D Scott; Srinivas, Sandy; Rini, Brian I; Bowman, Isaac; Pal, Sumanta K; Choueiri, Toni K; Heng, Daniel Y C; Deferred Cytoreductive Nephrectomy in Patients with Newly Diagnosed Metastatic Renal Cell Carcinoma.; European urology; 2020; vol. 78 (no. 4); 615-623

Study details

Study type	Retrospective cohort study
Study location	International mRCC Database Consortium (IMDC) databased used. This covers 33 centres in Canada, the USA, Belgium, Denmark, Germany, Greece, Italy, South Korea, Singapore, Japan, New Zealand, and Australia
Study dates	2006-2018
Sources of funding	No funding received
Inclusion criteria	first systemic therapy was sunitinib
Exclusion criteria	first treatment with sunitinib greater than12 months after diagnosis; unknown timings of deferred cytoreductive nephrectomy (CN); missing data on confounding variables
Intervention(s)	Deferred cytoreductive nephrectomy - followed by initial treatment with sunitinib; median time to receive CN after sunitinib was 7.8 months.
Comparator	SACT alone - first-line treatment with sunitinib
Outcome measures	Overall survival
Number of participants	Deferred CN arm - 85 SACT alone arm - 651
Duration of follow-up	Not reported - Median follow-up time for the survivors was 25 months (IQR 10–49)
Methods of analysis	Baseline cohort characteristics were compared between groups using the Kruskal-Wallis and the chi-square tests for continuous and categorical variables. Survival curves were plotted using the Kaplan-Meier method for OS outcomes, and were compared using the log-rank test. Multivariable Cox proportional hazards models were to adjust for the covariates for the deferred CN vs sunitinib alone arms. Furthermore, sensitivity analyses was carried out by using backward selection (with threshold for model inclusion set at $p < 0.05$) and the change-of-estimate approach (whereby only covariates that changed the main effect estimate by >10% were included) as a variable reduction strategy. A sensitivity analysis for unmeasured

	covariates was also conducted to evaluates the joint magnitude of the association between deferred CN and unmeasured confounders. Adjusted confounder: age at diagnosis, sex, year of diagnosis, Karnofsky performance status (>80 vs <80), IMDC risk group (intermediate vs poor risk), clear cell versus non–clear cell histology, sarcomatoid dedifferentiation, number of metastatic sites, and location of metastases (lung, brain, liver, bone, and lymph node).
Additional comments	Baseline data is reported for the overall participants included in the study and not for the population subsets.

Study arms

Deferred cytoreductive nephrectomy (N = 85)

SACT alone (N = 651)

Characteristics

Study-level characteristics

Characteristic	Study (N = 1541)
% Female Sample size	n = 403 ; % = 26
Age Median (IQR)	61 (54 to 68)
Primary RCC type - Clear cell histology Sample size	n = 1311 ; % = 85
Primary RCC type - Sarcomatoid dedifferentiation Sample size	n = 232 ; % = 15
Location of metastases - Brain Sample size	n = 130 ; % = 8
Location of metastases - lung Sample size	n = 1141 ; % = 74
Location of metastases - Liver Sample size	n = 333 ; % = 22

Characteristic	Study (N = 1541)
Location of metastases - bone Sample size	n = 593 ; % = 38
Location of metastases - Nodal Sample size	n = 785 ; % = 51
Location of metastases - Other Sample size	n = 461 ; % = 30

Outcomes

Overall survival

Outcome	Deferred cytoreductive nephrectomy vs SACT alone, , N2 = 85, N1 = 651
Overall survival Hazard ratio/95% CI	0.45 (0.33 to 0.6)

Overall survival - Polarity - Lower values are better

Critical appraisal - ROBIS checklist

Question	Answer
Risk of bias judgement	Serious *(Insufficient adjustment for confounders, limited reporting on missing data and protocol not identified)*
Directness	Directly applicable

Chakiryan, 2022

Bibliographic Reference	Chakiryan, Nicholas H; Gore, L Robert; Reich, Richard R; Dunn, Rodney L; Jiang, Da David; Gillis, Kyle A; Green, Elizabeth; Hajiran, Ali; Hugar, Lee; Zemp, Logan; Zhang, Jingsong; Jain, Rohit K; Chahoud, Jad; Spiess, Philippe E; Manley, Brandon J; Sexton, Wade J; Hollenbeck, Brent K; Gilbert, Scott M; Survival Outcomes Associated With Cytoreductive Nephrectomy in Patients With Metastatic Clear Cell Renal Cell Carcinoma.; JAMA network open; 2022; vol. 5 (no. 5); e2212347

Study details

Study type	Retrospective cohort study
Study location	United States - Uses the National Clinical Data Base (NCDB)

Study dates	January 2006 to December 2016
Sources of funding	NR
Inclusion criteria	clinical stage IV metastatic renal cancer at diagnosis; age of 18 to 100 years; availability of complete staging and demographic data; and receipt of targeted therapy as first-line treatment Diagnosis with clear cell renal cell carcinoma
Exclusion criteria	NCDB codes indicated that the patient was treated on an experimental or blinded clinical trial protocol; data were missing on distance from the patient's residence to the treating facility; if The International Metastatic Renal Cell Carcinoma Database risk score were not available in the NCDB, and available data points are not adequate to calculate this score directly
Intervention(s)	Deferred Cytoreductive nephrectomy (CN) - median time to nephrectomy after the first-line systemic therapy was 23 days with inter-quartile range of 68 to193 days; type of SACT not reported in the paper
Comparator	First line SACT only i.e no CN
Outcome measures	Overall survival
Number of participants	Overall - 12766 Deferred CN - 612 SACT alone - 7761
Duration of follow-up	From the date of diagnosis to death or censoring at last follow-up
Methods of analysis	Patients were stratified according to the CN status. Wilcoxon rank sum testing was used to compare continuous variables, and the $\chi 2$ test of independence was used to compare categorical variables. Kaplan-Meier estimates were used to generate survival functions. Propensity score matching carried out. Univariable analysis was repeated in the post-matching cohorts to assess for balance between groups. Subgroup analysis was conducted for each of the 3 methods (multivariable Cox proportional hazards regression, propensity score matching, and instrumental variable analysis). The results for OS outcome were extracted using the subgroup analysis using multivariable Cox regression model. Adjusted covariates: age, sex, race, Charlson-Deyo score, facility type, year of diagnosis, cT stage, cN stage, and cytoreductive nephrectomy status
Additional comments	Study included 12, 766 participants in total with 5,005 in the CN arm and 7,761 in no CN arm. The protocol relevant outcomes were extracted from the subset of the CN arm who received delayed CN compared to no CN arm (612 vs. 7,761) . However, the baseline data was not reported for this

	subset but as an overall for the participants who had received cytoreductive nephrectomy and was extracted (5,005 and 7,761). Study uses and reports the protocol relevant outcomes based on both multiple-cox regression and propensity score matching model. The extracted results came from the propensity score matching model.

Study arms

Cytoreductive nephrectomy (N = 5005)

Deferred Cytoreductive nephrectomy - 612

SACT alone (N = 7761)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy (N = 5005)	SACT alone (N = 7761)
% Female Sample size	n = 1540 ; % = 31	n = 2482 ; % = 32
Age Median (IQR)	61 (54 to 67)	65 (57 to 72)
TNM classification - cT1 Sample size	n = 887 ; % = 18	n = 2295 ; % = 30
TNM classification - cT2 Sample size	n = 1721 ; % = 34	n = 2213 ; % = 29
TNM classification - cT3 Sample size	n = 2049 ; % = 41	n = 2101 ; % = 27
TNM classification - cT4 Sample size	n = 348 ; % = 7	n = 1152 ; % = 15

Outcomes

Overall Survival

Outcome	Cytoreductive nephrectomy vs SACT alone, , N2 = 612, N1 = 7716
Overall survival Deferred cytoreductive nephrectomy Hazard ratio/95% CI	0.39 (0.36 to 0.43)

Overall survival - Polarity - Lower values are better

Critical appraisal - ROBIS checklist

Question	Answer
Risk of bias judgement	Serious *(Insufficient adjustment for confounders, limited reporting on missing data and protocol not identified)*
Directness	Directly applicable

Day, 2016

Bibliographic Reference	Day, D; Kanjanapan, Y; Kwan, E; Yip, D; Lawrentschuk, N; Davis, I D; Azad, A A; Wong, S; Rosenthal, M; Gibbs, P; Tran, B; Benefit from cytoreductive nephrectomy and the prognostic role of neutrophil-to-lymphocyte ratio in patients with metastatic renal cell carcinoma.; Internal medicine journal; 2016; vol. 46 (no. 11); 1291-1297

Study details

Study type	Retrospective cohort study
Study location	Australia - locally conducted at four Australian hospitals
Study dates	January 2006 - December 2012
Sources of funding	Institute of Health and Biomedical Innovation of Queensland University of Technology
Inclusion criteria	Patients with metastatic disease at diagnosis (de novo mRCC) and with complete information on survival and treatment data, neutrophil-to-lymphocyte ratio and other preoperative variables were included
Exclusion criteria	Patients who had received systemic therapy before 1 January 2006 were excluded
Intervention(s)	Cytoreductive nephrectomy who had received first-line systemic therapy. All participants received cytoreductive nephrectomy within 3 months of the diagnosis

Comparator	SACT alone i.e., no cytoreductive nephrectomy. (76 out of 91 received sunitinib, others received pazopanib, everolimus, bevacizumab, interferon and temsirolimus – treatment combinations unclear).
Outcome measures	Overall survival
Number of participants	Overall - 91 • Cytoreductive nephrectomy arm - 46 • No Cytoreductive nephrectomy arm - 45 Subset receiving SACT • Cytoreductive nephrectomy arm - 42 • No Cytoreductive nephrectomy arm (SACT alone) - 34
Duration of follow-up	NR
Methods of analysis	Descriptive statistics were used to summaries patient characteristics. Survival analyses were performed by calculating hazard ratios using the Cox proportional hazards model. Median survival was determined using the Kaplan–Meier method. Comparisons between groups were made using Fisher's exact test. Univariate analysis was used to determine the statistically significant factors for the overall survival. Adjustment was carried out for: Cytoreductive nephrectomy (CN), MSKCC risk classification, neutrophil-to-lymphocyte ratio, histology and systemic treatment.
Additional comments	Study included 91 participants in total. The protocol relevant outcomes were extracted from the subset of participants who had the history of receiving systemic therapy with or without cytoreductive nephrectomy (42 and 34 participants). However, the baseline data was not reported for this subset but as an overall for the participants who had or not had cytoreductive nephrectomy (46 and 45).

Study arms

Cytoreductive nephrectomy (N = 46)

No Cytoreductive nephrectomy (N = 45)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy (N = 46)	No Cytoreductive nephrectomy (N = 45)
Age (years) Median (IQR)	59 (NR to NR)	64.6 (NR to NR)
Intervention subtype - Sunitinib Sample size	n = 33 ; % = 72	n = 34 ; % = 76
Intervention subtype - Pazopanib Sample size	n = 4 ; % = 9	n = 0 ; % = 0
Intervention subtype - Everolimus Sample size	n = 0 ; % = 0	n = 4 ; % = 9
Intervention subtype - Bevacizumab Sample size	n = 2 ; % = 4	n = 0 ; % = 0
Intervention subtype - Interferon Sample size	n = 2 ; % = 4	n = 0 ; % = 0
Intervention subtype - Temsirolimus Sample size	n = 1 ; % = 2	n = 0 ; % = 0
Primary RCC type - Clear cell histology Sample size	n = 37 ; % = 80	n = 27 ; % = 60
Primary RCC type - Non-clear cell histology Sample size	n = 6 ; % = 13	n = 5 ; % = 11
Primary RCC type - unknown Sample size	n = 3 ; % = 7	n = 13 ; % = 29

Outcomes

Overall survival

Outcome	Cytoreductive nephrectomy vs No Cytoreductive nephrectomy, , N2 = 42, N1 = 34
Overall survival Hazard ratio/95% CI	0.41 (0.19 to 0.6)

Overall survival - Polarity - Lower values are better

Critical appraisal - ROBIS checklist

Question	Answer
Risk of bias judgement	Serious *(No adjustment for confounders or matching undertaken. Limited information about missing data or inclusion criteria. No protocol identified so unable to fully assess bias in selection of reported result.)*
Directness	Directly applicable

Dragomir, 2022

Bibliographic Reference	Dragomir, A.; Nazha, S.; Tanguay, S.; Breau, R.H.; Bhindi, B.; Rendon, R.A.; Kapoor, A.; Hotte, S.J.; Basappa, N.; Fairey, A.; So, A.I.; Kollmannsberger, C.; Finelli, A.; Hansen, A.; Canil, C.; Heng, D.; Lattouf, J.-B.; Bjarnason, G.; Power, N.; Pouliot, F.; Wood, L.A.; Outcomes of Cytoreductive Nephrectomy for Patients with Metastatic Renal Cell Carcinoma: Real World Data from Canadian Centers; European Urology Focus; 2022; vol. 8 (no. 6); 1703-1710

Study details

Study type	Retrospective cohort study
Study location	Canada - Data retrieved from the Canadian Kidney Cancer information system (CKCis)
Study dates	January 2011 and April 2020
Sources of funding	None
Inclusion criteria	Diagnosis of RCC was made on the basis of histopathological evaluations; patients with synchronous disease (i.e, metastases found 3 months before or within 6 months after the primary tumour diagnosis); treated (with cytoreductive nephrectomy (CN) or/and systemic therapy (ST)) within 12 months of the initial RCC diagnosis Edit: IMDC intermediate or high risk

Exclusion criteria	patients who had indolent metastatic disease
Intervention(s)	Deferred Cytoreductive nephrectomy after systemic therapy
Comparator	Systemic therapy alone (overall across the study, 51% had sunitinib, others had pazopanib, ipilimumab / nivolumab combination, or other).
Outcome measures	Overall survival
Number of participants	Overall n= 325 Intervention arm (CN) - 73 Comparator arm (SACT alone) - 252
Duration of follow-up	Earliest date of death, loss to follow-up, or the end of the study period (April 2020)
Methods of analysis	Frequency and percentage for categorical variables and as the median with interquartile range for continuous variables; Chi-square test or Fisher's exact test for categorical variables for categorical variables; non-parametric Wilcoxon rank-sum test was used for continuous variables. Kaplan Meier curve analysis was performed to estimate OS from the index date until death (any causes) or loss to follow-up. A log-rank test was used to evaluate differences in overall survival. Uses IPTW to account for the differences in the distribution among baseline characteristics. Adjusted confounders: Age, sex, sites and number of organs for metastasis, cell histology, IMDC risk and Charlson comorbidity index
Additional comments	

Study arms

Cytoreductive nephrectomy (N = 73)

After SACT

SACT alone (N = 252)

Characteristics

Arm-level characteristics

Characteristic	Cytoreductive nephrectomy (N = 73)	SACT alone (N = 252)
% Female Sample size	n = 19 ; % = 26	n = 184 ; % = 27

Characteristic	Cytoreductive nephrectomy (N = 73)	SACT alone (N = 252)
Age (Years (IQR)) Median (IQR)	62 (55 to 68)	64 (57 to 70)
Intervention subtype - Sunitinib Sample size	n = 52 ; % = 71.2	n = 121 ; % = 48
Intervention subtype - Pazopanib Sample size	n = 8 ; % = 11	n = 52 ; % = 20.6
Intervention subtype - Ipilimumab/nivolumab Sample size	n = 3 ; % = 4.1	n = 57 ; % = 22.6
Intervention subtype - Others Nivolumab, everolimus, pembrolizumab, temsirolimus, atezolizumab, axitinib, lenvatinib Sample size	n = 10 ; % = 13.7	n = 22 ; % = 8.8
Primary RCC type - Clear-cell RCC Sample size	n = 61 ; % = 83.6	n = 169 ; % = 67.1
Location of metastases - lung Sample size	n = 39 ; % = 53.4	n = 135 ; % = 53.6
Location of metastases - bone Sample size	n = 14 ; % = 19.2	n = 66 ; % = 26.2
Location of metastases - Brain Sample size	n = 2 ; % = 2.7	n = 16 ; % = 6.4
Location of metastases - Adrenal gland Sample size	n = 10 ; % = 13.7	n = 29 ; % = 11.5
Location of metastases - Liver Sample size	n = 9 ; % = 12.3	n = 41 ; % = 16.3
Location of metastases - Lymph nodes Sample size	n = 28 ; % = 38.4	n = 104 ; % = 41.3

Outcomes

Overall Survival

Outcome	Cytoreductive nephrectomy vs SACT alone, , N2 = 73, N1 = 252
Overall survival Hazard ratio/95% CI	0.41 (0.28 to 0.6)

Overall survival - Polarity - Lower values are better

Critical appraisal - ROBIS checklist

Question	Answer
Risk of bias judgement	Serious *(No adjustment for confounders or matching undertaken. Limited information about missing data or inclusion criteria. No protocol identified so unable to fully assess bias in selection of reported result.)*
Directness	Directly applicable

Fransen van de Putte, 2023

Bibliographic Reference	Fransen van de Putte, Elisabeth E; van den Brink, Luna; Mansour, Mohamed A; van der Mijn, Johannes C; Wilgenhof, Sofie; van Thienen, Johannes V; Haanen, John B A G; Boleti, Ekaterini; Powles, Thomas; Zondervan, Patricia J; Graafland, Niels M; Bex, Axel; Indications and Outcomes for Deferred Cytoreductive Nephrectomy Following Immune Checkpoint Inhibitor Combination Therapy: Can Systemic Therapy be Withdrawn in Patients with No Evidence of Disease?.; European urology open science; 2023; vol. 55; 15-22

Study details

Study type	Retrospective cohort study
Study location	Four European centres; two in Netherlands and two in England
Study dates	March 2019 - June 2022
Sources of funding	No funding received
Inclusion criteria	Biopsy-confirmed synchronous metastatic renal cell carcinoma; receiving first-line ipilimumab-nivolumab
Intervention(s)	Deferred cytoreductive nephrectomy
Comparator	SACT alone - receiving first-line ICI therapy (ipilimumab-nivolumab)
Outcome measures	Cancer-specific survival

Number of participants	Deferred cytoreductive nephrectomy - 19 SACT alone - 7
Duration of follow-up	3 years
Loss to follow-up	No loss to follow up
Methods of analysis	Kaplan-Meier data for disease-free survival, progression-free survival, and cancer-specific survival were compared between IMDC risk groups and between modalities using log-rank tests
Additional comments	Study included 125 participants in total. The protocol relevant outcomes were extracted from the subset of participants who had near complete or complete response to at the metastatic site (a >80% reduction in the cumulative metastatic volume) with or without cytoreductive nephrectomy (19 and 7 participants). However, the baseline data was not reported for this subset but as an overall for the participants who had or not had cytoreductive nephrectomy (23 and 7).

Study arms

Deferred Cytoreductive nephrectomy (N = 23)

SACT (N = 7)

Characteristics

Arm-level characteristics

Characteristic	Deferred Cytoreductive nephrectomy (N = 23)	SACT (N = 7)
% Female Sample size	n = 10 ; % = 43	n = 3 ; % = 42
Age Mean (SD)	62 (10)	71 (12)
Primary RCC type - Papillary type 2 Sample size	n = 0 ; % = 0	n = 1 ; % = 14
Primary RCC type - Clear cell RCC with sarcomatoid variant Sample size	n = 1 ; % = 4	n = 1 ; % = 14
Primary RCC type - Clear cell RCC with other variant Sample size	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	Deferred Cytoreductive nephrectomy (N = 23)	SACT (N = 7)
Primary RCC type - Poorly differentiated Sample size	n = 0 ; % = 0	n = 1 ; % = 14
Primary RCC type - clear cell RCC Sample size	n = 21 ; % = 92	n = 4 ; % = 57
Primary RCC type - Sarcomatoid Sample size	n = 1 ; % = 4	n = 0 ; % = 0
Baseline performance status - 0 () ECOG performance status Sample size	n = 12 ; % = 52	n = 2 ; % = 29
Baseline performance status - 1 () ECOG performance status Sample size	n = 9 ; % = 39	n = 5 ; % = 71
Baseline performance status - ≥ 2 ECOG performance status Sample size	n = 1 ; % = 4	n = 0 ; % = 0
Baseline performance status - Unknown ECOG performance status Sample size	n = 2 ; % = 9	n = 0 ; % = 0

Outcomes

Cancer specific mortality

Outcome	Deferred Cytoreductive nephrectomy , , N = 19	SACT, , N = 7
Cancer specific mortality At 3 years No of events	n = 15 ; % = 80	n = 7 ; % = 100

Cancer specific mortality - Polarity - Lower values are better

Critical appraisal - ROBIS checklist

Question	Answer
Risk of bias judgement	Serious *(No adjustment for confounders or matching undertaken. Limited information about missing data or inclusion criteria. No protocol identified so unable to fully assess bias in selection of reported result.)*
Directness	Directly applicable

Hatakeyama, 2021

Bibliographic Reference	Hatakeyama, Shingo; Naito, Sei; Numakura, Kazuyuki; Kato, Renpei; Koguchi, Tomoyuki; Kojima, Takahiro; Kawasaki, Yoshihide; Kandori, Shuya; Kawamura, Sadafumi; Tsushima, Eiki; Nishiyama, Hiroyuki; Ito, Akihiro; Kojima, Yoshiyuki; Habuchi, Tomonori; Obara, Wataru; Tsuchiya, Norihiko; Ohyama, Chikara; Impact of cytoreductive nephrectomy in patients with primary metastatic renal cell carcinoma receiving systemic tyrosine kinase inhibitor therapy: A multicenter retrospective study.; International journal of urology : official journal of the Japanese Urological Association; 2021; vol. 28 (no. 4); 369-375

Study details

Study type	Retrospective cohort study
Study location	Japan - Michinoku Japan Urological Cancer Study Group database
Study dates	January 2008 - November 2019
Sources of funding	Japan Society for the Promotion of Science
Inclusion criteria	Patients with primary metastatic RCC initially treated with frst-line sunitinib, sorafenib, axitinib, and pazopanib were included
Exclusion criteria	Treatment with frst-line interferon, mammalian target of rapamycin inhibitors, immunotherapy, or chemotherapy; a period from diagnosis to first treatment (TKIs or immediate CN) of more than 3 months; a period of surveillance after immediate CN of more than 3 months; a follow-up period from the first treatment of less than 3 months; and missing data on confounder variables
Intervention(s)	Deferred cytoreductive nephrectomy - after receiving tyrosine kinase inhibitors (TKI); Median time to CN was 5.1 months with inter-quartile range of 3.5-6.3 months
Comparator	SACT alone - TKI

Outcome measures	Overall survival
Number of participants	Overall n= 171 Deferred CN - 39 SACT only - 132
Duration of follow-up	Until death
Methods of analysis	Quantitative variables were expressed as median values with IQRs; intergroup difference was tested using Student's t-test or the Mann–Whitney U-test to compare continuous variables; Fisher's exact test or the chi-squared test was used to compare categorical variables; and OS from the initial treatment until death was estimated using Kaplan–Meier curves and the log rank test. Uses inverse probability of treatment weighting (IPTW) -adjusted Cox regression analysis. Adjusted confounders - age, sex, performance status, number of IMDC risk factors, clinical stage (cT3b–4), and number of metastatic organs

Study arms

Deferred cytoreductive nephrectomy (N = 39)

SACT (N = 132)

Characteristics

Arm-level characteristics

Characteristic	Deferred cytoreductive nephrectomy (N = 39)	SACT (N = 132)
% Female Sample size	n = 17 ; % = 44	n = 32 ; % = 24
Age Median (IQR)	67 (62 to 72)	67 (61 to 76)
Intervention subtype - Sunitinib Sample size	n = 17 ; % = 44	n = 65 ; % = 49
Intervention subtype - Sorafenib Sample size	n = 2 ; % = 5.2	n = 16 ; % = 12

Characteristic	Deferred cytoreductive nephrectomy (N = 39)	SACT (N = 132)
Intervention subtype - Axitinib Sample size	n = 19 ; % = 49	n = 47 ; % = 36
Intervention subtype - Pazopanib Sample size	n = 1 ; % = 2.6	n = 4 ; % = 3
TNM classification - T1-2 Sample size	n = 14 ; % = 36	n = 32 ; % = 24
TNM classification - T3a Sample size	n = 8 ; % = 21	n = 34 ; % = 26
TNM classification - T3b-4 Sample size	n = 17 ; % = 44	n = 63 ; % = 48
TNM classification - Unknown Sample size	n = 0 ; % = 0	n = 3 ; % = 2
Location of metastases - lung Sample size	n = 23 ; % = 59	n = 77 ; % = 58
Location of metastases - Distant lymph node Sample size	n = 11 ; % = 28	n = 49 ; % = 37
Location of metastases - bone Sample size	n = 14 ; % = 36	n = 38 ; % = 29
Location of metastases - Liver Sample size	n = 3 ; % = 8	n = 23 ; % = 17
Location of metastases - Adrenal Sample size	n = 1 ; % = 3	n = 16 ; % = 12
Location of metastases - Brain Sample size	n = 2 ; % = 5	n = 9 ; % = 7
Location of metastases - Pancreas Sample size	n = 0 ; % = 0	n = 5 ; % = 4

Characteristic	Deferred cytoreductive nephrectomy (N = 39)	SACT (N = 132)
Location of metastases - Others Sample size	n = 8 ; % = 21	n = 46 ; % = 35
Location of metastases - Nonclear histology Sample size	n = 3 ; % = 7.7	n = 21 ; % = 16
Baseline performance status Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Overall survival

Outcome	Deferred cytoreductive nephrectomy vs SACT, , N2 = 39, N1 = 132
Overall survival deferred cytoreductive nephrectomy vs. SACT alone Hazard ratio/95% CI	0.34 (0.2 to 0.61)

Overall survival - Polarity - Lower values are better

Critical appraisal - ROBIS checklist

Question	Answer
Risk of bias judgement	Moderate *(Insufficient adjustment for confounders)*
Directness	Directly applicable

Appendix E – Forest plots

Review H1: Upfront cytoreductive nephrectomy (CN) vs. deferred CN

Survival outcomes

Figure 1. Progression-free survival, ≤5 years - Clear cell - Randomised controlled trial

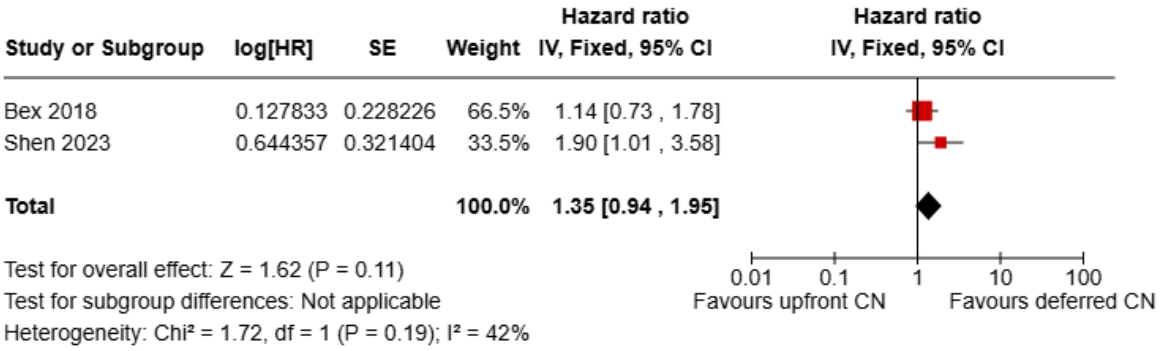


Figure 2. Overall survival, ≤5 years - Clear cell population - Randomised controlled trial

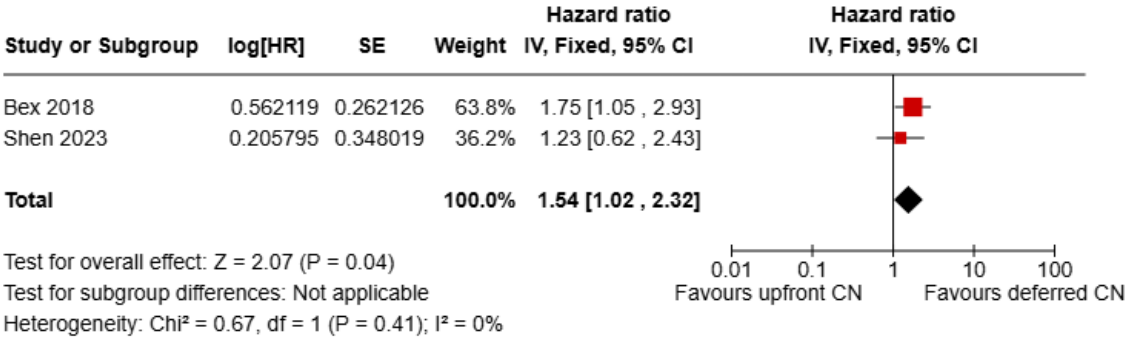
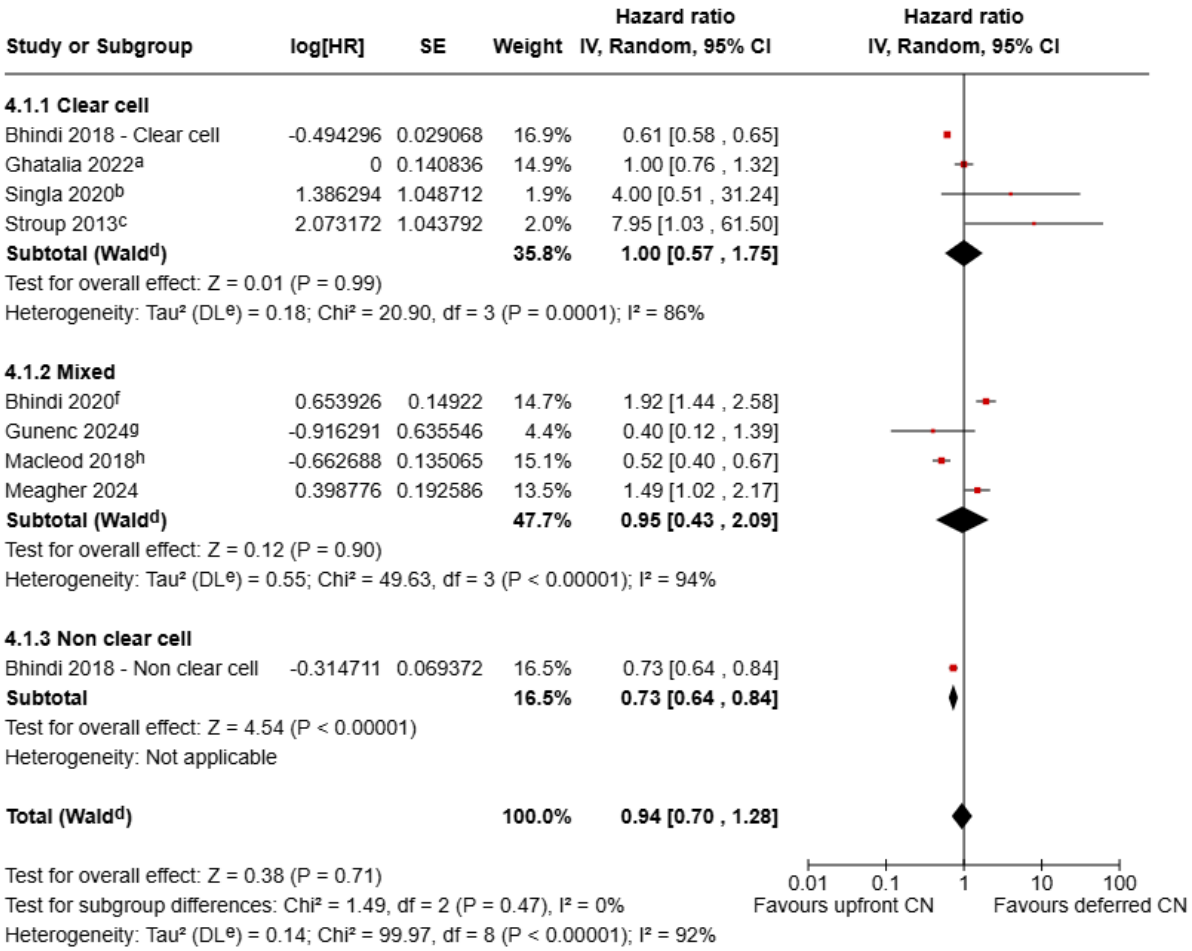


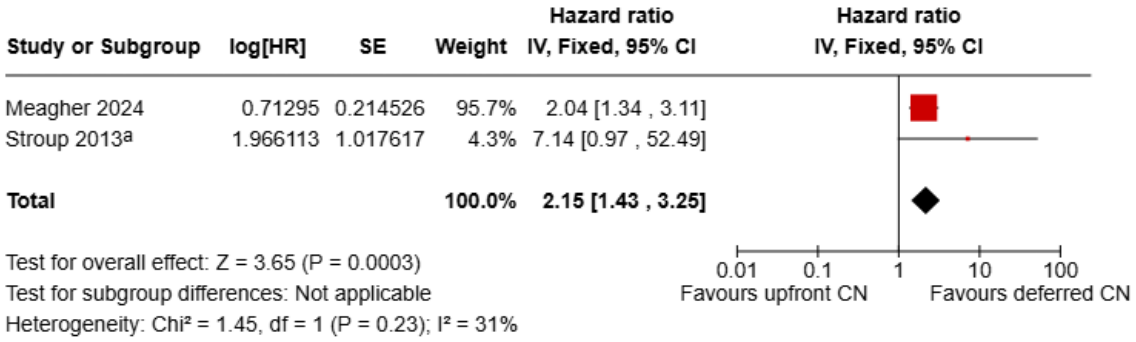
Figure 3. Overall survival, ≤5 years - Mixed population – Non-randomised controlled trial



Footnotes

[a]Follow-up was not reported
[b]Median follow-up was 14.7 months
[c]Median follow-up was 4.6 months (sunitinib); 22.8 months (sunitinib + CN)
[d]CI calculated by Wald-type method.
[e]Tau² calculated by DerSimonian and Laird method.
[f]Median follow-up was 25 months
[g]Median follow-up was 21 months
[h]Median follow-up was 12 months

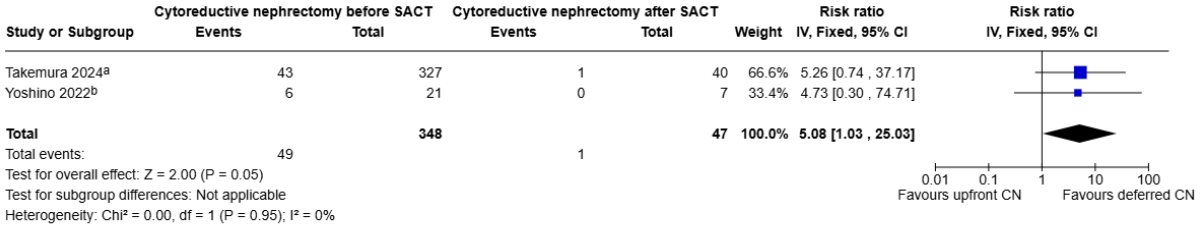
Figure 4. Cancer specific survival, ≤5 years - Clear cell population - Non-randomised controlled trial



Footnotes

[a]Median follow-up was 4.6 months (sunitinib); 22.8 months (sunitinib + CN)

Figure 5. Mortality, ≤5 years - Mixed population - Non-randomised controlled trial



Footnotes

[a]Median follow-up was 12 months

[b]Converted from 'overall survival' reported as events; median follow-up was 12.0 months

All other outcomes

Figure 6. Adverse Events grade ≥ 3 (Clavien Dindo) - Clear cell population - Non-randomised controlled trial

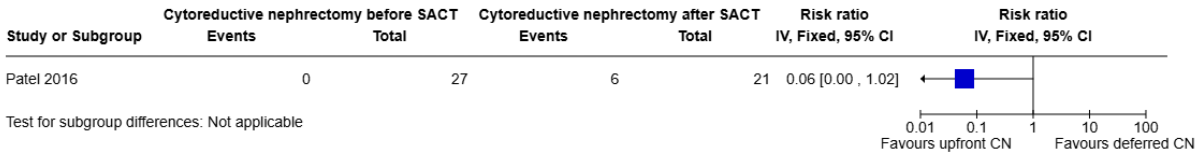


Figure 7. Duration of hospital stay (days) - Clear cell - Randomised controlled trial

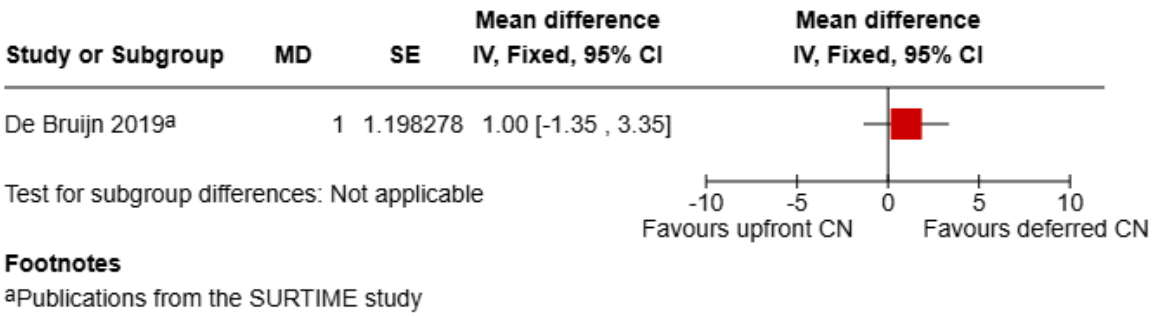


Figure 8. Adverse Events grade ≥ 3 (Clavien Dindo) - Clear cell population - Non-randomised controlled trial

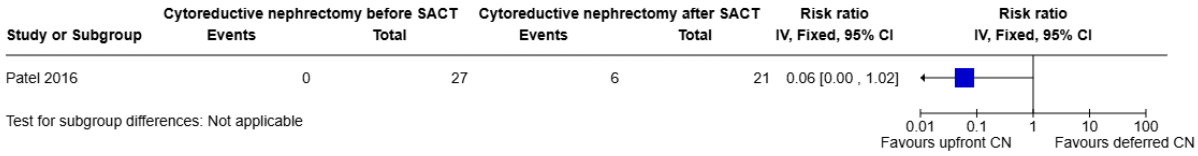
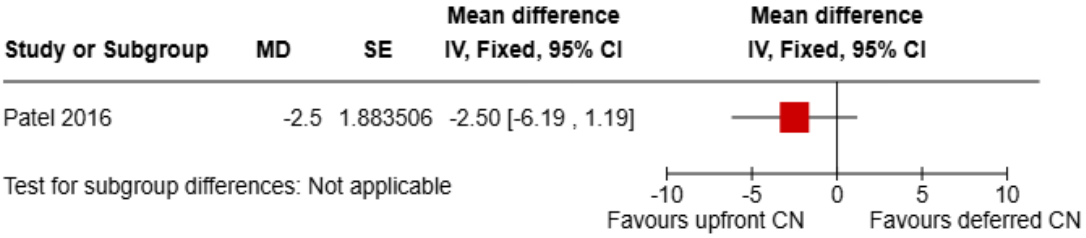


Figure 9. Duration of hospital stay (days) - Clear cell - Non-randomised controlled trial



Review H1: Upfront cytoreductive nephrectomy (CN) vs. systemic anti-cancer therapy (SACT) alone

Survival outcomes

Figure 10. Progression-free survival, ≤5 years - Clear cell - Randomised controlled trial

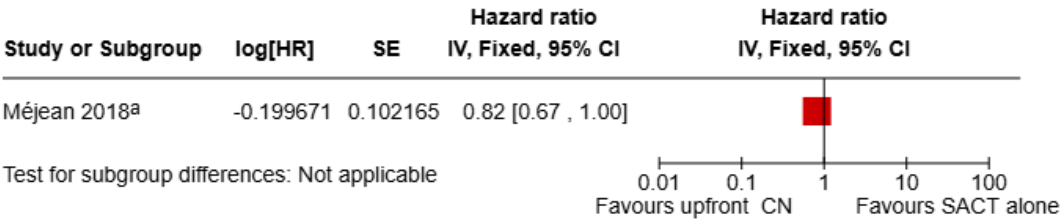
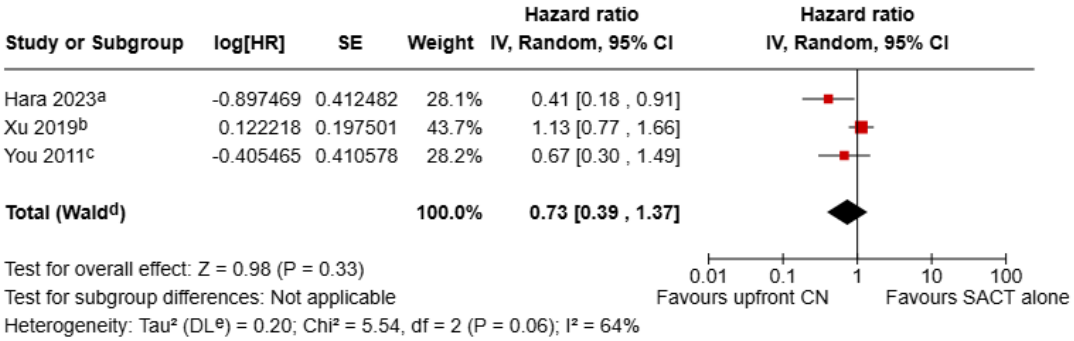


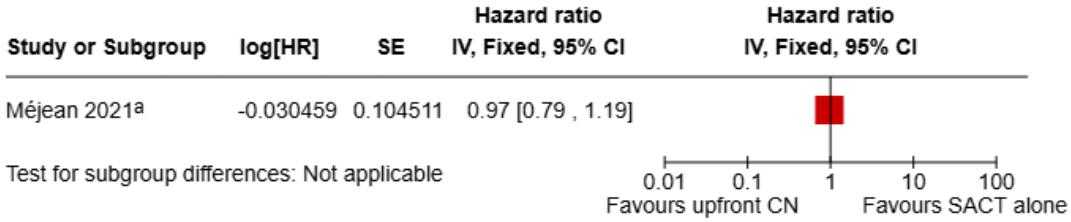
Figure 11. Progression-free survival, ≤5 years - Clear cell - Non-randomised controlled trial



Footnotes

[a]Median follow-up was 15.7 months
[b]Last day of follow-up (8th July 2018)
[c]Follow-up not reported
[d]CI calculated by Wald-type method.
[e]Tau² calculated by DerSimonian and Laird method.

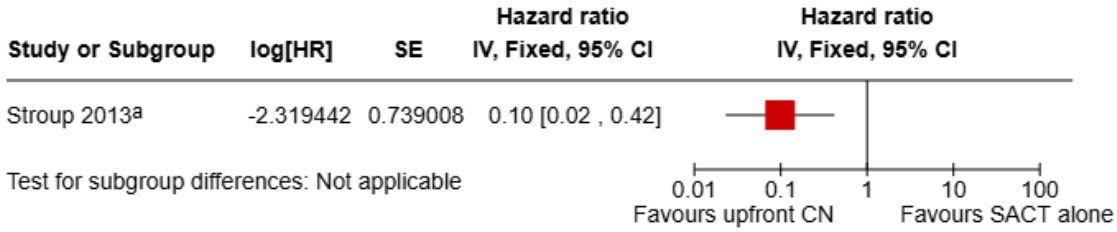
Figure 12. Overall survival, ≤5 years - Clear cell population - Randomised controlled trial



Footnotes

[a]Median follow-up was 36.6 months; publications from the CARMENA study

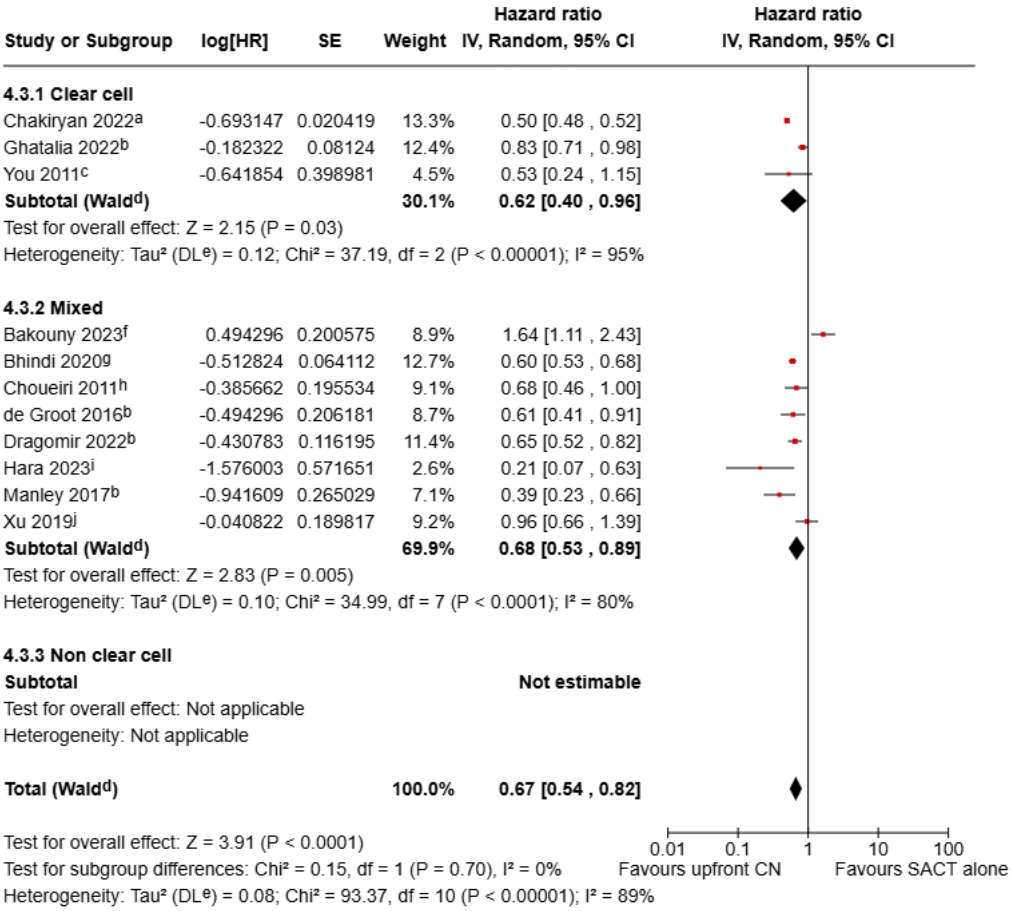
Figure 13. Cancer specific survival, ≤5 years - Clear cell population - Non-randomised controlled trial



Footnotes

[a]Median follow-up was 4.6 months (sunitinib); 22.8 months (sunitinib + CN)

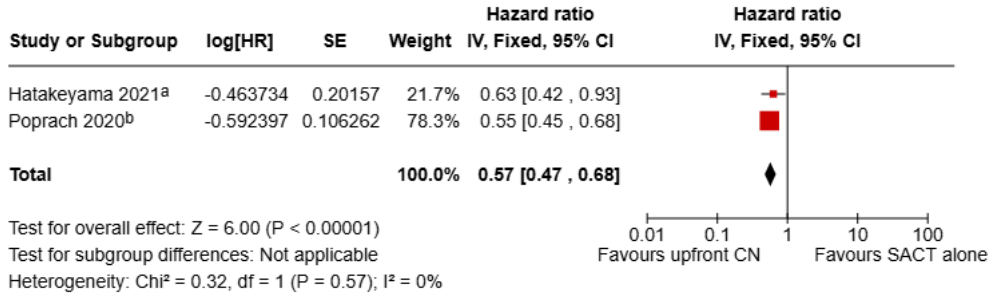
Figure 14. Overall survival, ≤5 years - Clear cell/mixed population - Non-randomised controlled trial



Footnotes

[a]Median follow-up was 36.0 months
[b]Follow-up was not reported
[c]Follow-up not reported
[d]CI calculated by Wald-type method.
[e]Tau² calculated by DerSimonian and Laird method.
[f]Median follow-up was 12 months
[g]Median follow-up was 25 months
[h]Median follow-up was 16.3 months
[i]Median follow-up was 15.7 months
[j]Last day of follow-up (8th July 2018)

Figure 15. Overall survival, >5 years - Mixed population - Non-randomised controlled trial

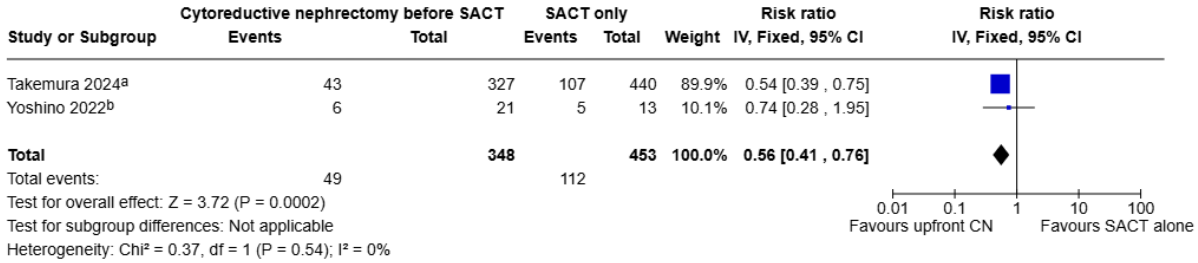


Footnotes

[a]Exact follow-up period was not reported

[b]Follow-up was not reported

Figure 16. Mortality, ≤5 years - Mixed population - Non-randomised controlled trial



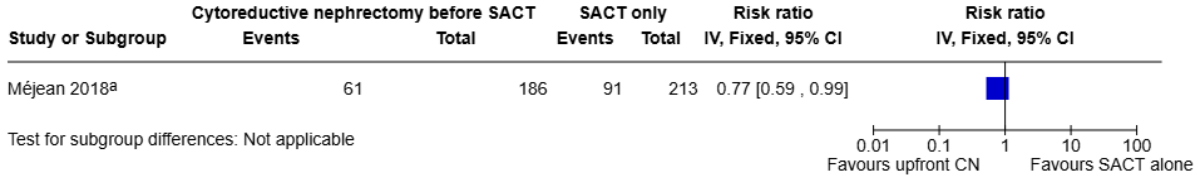
Footnotes

[a]Median follow-up was 12 months

[b]Converted from 'overall survival' reported as events; median follow-up was 12.0 months

All other outcomes

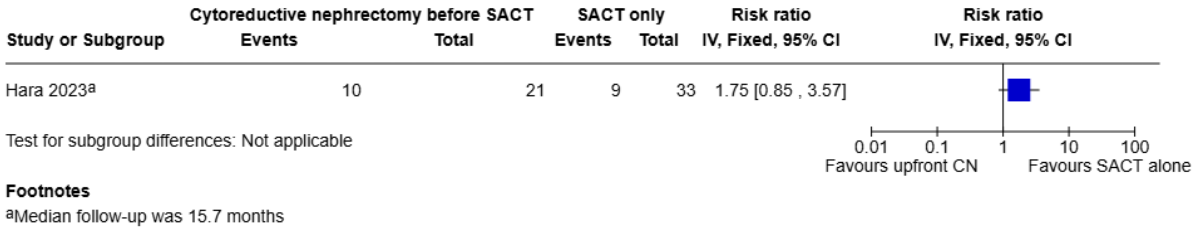
Figure 17. Adverse Events grade ≥ 3 - Mixed population - Randomised controlled trial



Footnotes

[a]Median follow-up was 50.9 months; publications from the CARMENA study

Figure 18. Adverse Events grade ≥ 3 - Mixed population - Non-randomised controlled trial

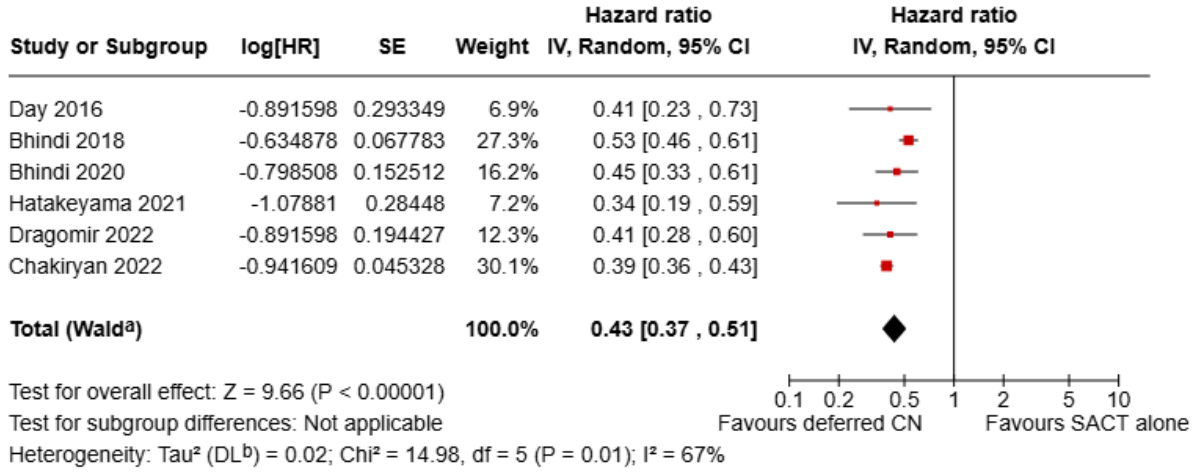


Footnotes

[a]Median follow-up was 15.7 months

Review H2: Deferred cytoreductive nephrectomy (CN) vs. systemic anti-cancer therapy (SACT) alone

Figure 19. Overall survival ≤ 5 years



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Appendix F – GRADE tables

Review H1

Upfront cytoreductive nephrectomy (CN) vs. deferred CN

Survival outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Upfront CN + SACT**	**Deferred CN**	**Relative (95% CI)**	**Absolute (95% CI)**	
Progression-free survival, ≤5 years – Clear cell population											
2 (Bex 2028, Shen 2023)	randomised studies	serious [a]	serious[b]	not serious	very serious[c,d]	none	92	91	HR 1.35 (0.94 to 1.95)	NR	Very low
1 (Gunenc 2024)	non-randomised studies	Serious [a]	Serious[g]	not serious	very serious[c,d]	none	13	38	HR 0.40 (0.12 to 1.39)	NR	Very low
Overall survival, ≤5 years - Clear cell population											
2 (Bex 2028, Shen 2023)	randomised studies	serious [a]	not serious	not serious	serious[d]	none	92	91	HR 1.54 (1.02 to 2.32)	NR	Low
Overall survival, ≤5 years – Mixed population											
8 (Bhindi 2018, Bhindi 2020, Ghatalia 2022, Gunenc	non-randomised studies	very serious [e]	very serious[f]	not serious	serious[c]	none	8699	9032	HR 0.94 (0.70 to 1.28)	NR	Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Upfront CN + SACT**	**Deferred CN**	**Relative (95% CI)**	**Absolute (95% CI)**	
2024, Macleod 2018, Meagher 2024, Singla 2020, Stroup 2013)											
Overall survival, >5 years – Mixed population											
1 (Hatakeyama 2021)	non-randomised studies	very serious[e]	serious[g]	not serious	very serious[c,d]	none	107	39	HR 1.64 (0.87 to 3.09)	NR	Very low
Cancer specific survival, ≤5 years - Clear cell population											
2 (Meagher 2024, Stroup 2013)	non-randomised studies	very serious[e]	not serious	not serious	Serious[d]	none	158	59	HR 2.15 (1.43 to 3.25)	NR	Very low
Mortality, ≤5 years – Mixed population											
2 (Takemura 2024, Yoshino 2022*)	non-randomised studies	very serious[e]	not serious	not serious	serious[d]	none	49/348 (14.1%)	1/47 (2.1%)	RR 5.08 (1.03 to 25.03)	NR	Very low

CN: cytoreductive nephrectomy; **CI:** confidence interval; **HR:** hazard ratio; **NR:** not reported; **RR:** risk ratio; **SACT:** systemic anti-cancer therapy

Explanations

a. Downgraded once for risk of bias. Greater than 50% of the weight in meta-analysis came from studies with some concerns or high risk of bias
b. Downgraded once for inconsistency. I^2 was between 40% and 60%
c. Downgraded once for imprecision. 95% confidence interval for the effect size crossed the line of no effect

d. Downgraded once for imprecision. Result comes from a study with a small sample size (sample size <576 participants)
e. Downgraded twice for risk of bias. Greater than 50% of the weight in meta-analysis came from studies at high risk of bias
f. Downgraded twice for inconsistency. I^2 greater than 60%
g. Downgraded once for inconsistency. Single study only

All other outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Upfront CN + SACT**	**Deferred CN**	**Relative (95% CI)**	**Absolute (95% CI)**	
Adverse events grade ≥3 (Clavien Dindo) – Clear cell population											
1 (Bex 2018)	randomised trials	serious[a]	serious[b]	not serious	very serious[c,d]	none	1/34 (2.9%)	3/46 (6.5%)	RR 0.45 (0.05 to 4.15)	NR	Very low
Adverse events grade ≥3 (Clavien Dindo) – Clear cell population											
1 (Patel 2016)	non-randomised studies	very serious[e]	serious[b]	not serious	very serious[c,d]	none	0/27 (0.0%)	6/21 (28.6%)	RR 0.06 (0.00 to 1.02)	NR	Very low
Duration of hospital stay (days) – Clear cell population											
1 (De Bruijn 2019)	randomised trials	serious[a]	serious[b]	not serious	very serious[c,d]	none	46	34	NR	MD 1 higher (1.35 lower to 3.35 higher)	Very low
Duration of hospital stay (days) – Clear cell population											
1 (Patel 2016)	non-randomised studies	very serious[e]	serious[b]	not serious	very serious[c,d]	none	27	21	NR	MD 2.5 lower (6.19 lower to 1.19 higher)	Very low

CN: cytoreductive nephrectomy; **CI:** confidence interval; **MD:** mean difference; **NR:** not reported; **RR:** risk ratio; **SACT:** systemic anti-cancer therapy

Explanations

a. Downgraded once for risk of bias. Greater than 50% of the weight in meta-analysis came from studies with some concerns or high risk of bias
b. Downgraded once for inconsistency. Analysis included a single study
c. Downgraded once for imprecision. 95% confidence interval for the effect size crossed the line of no effect
d. Downgraded once for imprecision. Result comes from a study with a small sample size (sample size <576 participants)
e. Downgraded twice for risk of bias. Greater than 50% of the weight in meta-analysis came from studies at serious or high risk of bias

Upfront cytoreductive nephrectomy (CN) vs. systemic anti-cancer therapy (SACT) alone

Survival outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Upfront CN + SACT**	**SACT alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
Progression-free survival, ≤5 years – Clear cell population											
1 (Méjean 2018)	randomised trials	serious[a]	serious[b]	not serious	very serious[c,d]	None	226	224	HR 0.82 (0.67 to 1.00)	NR	Very low
Progression-free survival, ≤5 years - Clear cell population											
3 (Hara 2023, Xu 2019, You 2011)	non-randomised studies	very serious[e]	serious[f]	not serious	very serious[c,d]	None	136	114	HR 0.73 (0.39 to 1.37)	NR	Very low
Overall survival, ≤5 years – Clear cell population											
1 (Méjean 2018)	randomised trials	serious[a]	serious[b]	not serious	serious[c]	None	226	224	HR 0.97 (0.79 to 1.19)	NR	Very low
Overall survival, ≤5 years - Mixed population											
11 (Bakouny 2023, Bhindi 2020,	non-randomised studies	very serious[e]	very serious[f]	not serious	not serious	None	6918	10174	HR 0.67 (0.54 to 0.82)	NR	Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Upfront CN + SACT**	**SACT alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
Chakiryan 2022, Choueiri 2011, Dragomir 2022, de Groot 2016, Ghatalia 2022, Hara 2023, Manley 2017, Xu 2019, You 2011)											
Overall survival, >5 years – Mixed population											
2 (Hatakeyama 2021, Poprach 2020)	non-randomised studies	very serious[e]	not serious	not serious	not serious	None	565	404	HR 0.57 (0.47 to 0.68)	NR	Low
Cancer specific survival, ≤5 years - Clear cell population											
1 (Stroup 2013)	non-randomised studies	serious[e]	serious[b]	not serious	serious[d]	None	17	7	HR 0.10 (0.02 to 0.42)	NR	Very low
Mortality, ≤5 years – Mixed population											
2 (Takemura 2024, Yoshino 2022)	non-randomised studies	very serious[e]	not serious	not serious	not serious	none	49/348 (14.1%)	112/453 (24.7%)	RR 0.56 (0.41 to 0.76)	NR	Low

CN: cytoreductive nephrectomy; **CI:** confidence interval; **HR:** hazard ratio; **NR:** not reported; **RR:** risk ratio; **SACT:** systemic anti-cancer therapy

Explanations

a. Downgraded once for risk of bias. Greater than 50% of the weight in meta-analysis came from studies with some concerns or high risk of bias
b. Downgraded once for inconsistency. Analysis included a single study.
c. Downgraded once for imprecision. 95% confidence interval for the effect size crossed the line of no effect
d. Downgraded once for imprecision. Result comes from a study with a small sample size (sample size <576 participants)
e. Downgraded twice for imprecision. Greater than 50% of the weight in meta-analysis came from studies at serious or high risk of bias
f. Downgraded twice for inconsistency. I^2 greater than 60%.

All other outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Upfront CN + SACT**	**SACT alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
Adverse events grade ≥3 (Clavien Dindo) – Mixed population											
1 (Méjean 2018)	randomised trials	serious[a]	serious[b]	not serious	serious[c]	none	61/186 (32.8%)	91/213 (42.7%)	RR 0.77 (0.59 to 0.99)	NR	Very low
Adverse events grade ≥3 (Clavien Dindo)– Mixed population											
1 (Hara 2023)	non-randomised studies	very serious[d]	serious[b]	not serious	very serious[c,e]	none	10/21 (47.6%)	9/33 (27.3%)	RR 1.75 (0.85 to 3.57)	NR	Very low

CN: cytoreductive nephrectomy; **CI:** confidence interval; **NR:** not reported; **RR:** risk ratio; **SACT:** systemic anti-cancer therapy

Explanations

a. Downgraded once for risk of bias. Greater than 50% of the weight in meta-analysis came from studies with some concerns or high risk of bias
b. Downgraded once for inconsistency. I2 was between 40% and 60%
c. Downgraded once for imprecision. 95% confidence interval for the effect size crossed the line of no effect
d. Greater than 50% of the weight in meta-analysis came from studies at serious or high risk of bias
e. Result comes from a study with a small sample size (sample size <576 participants)

Deferred cytoreductive nephrectomy (CN) vs. systemic anti-cancer therapy (SACT) alone

Table 13 Overall survival

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Deferred CN**	**SACT alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
Overall survival ≤ 5 years											
6 (Bhindi 2018, Bhindi 2020, Chakiryan 2022, Day 2016, Dragomir 2022, Hatakeyama 2021)	non-randomised studies	very serious[a]	not serious	not serious	not serious	none	8,464	8,692[b]	HR 0.43 (0.37 to 0.51)	NR	Low

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio; **NR:** not reported

Explanations

a. Downgraded twice for risk of bias. Greater than 50% of the weight in meta-analysis came from studies at high risk of bias
b. Bhindi et al. 2018 does not report number of participants in SACT alone arm.

Table 14 Cancer-specific mortality

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Deferred CN**	**SACT alone**	**Relative (95% CI)**	**Absolute (95% CI)**	
1 (Fransen 2023)	non-randomised studies	very serious[a]	serious[b]	not serious	very serious[c,d]	none	15/19 (78.9%)	7/7 (100.0%)	RR 0.83 (0.61 to 1.11)	170 fewer per 1,000 (from 390 fewer to 110 more)	Very low

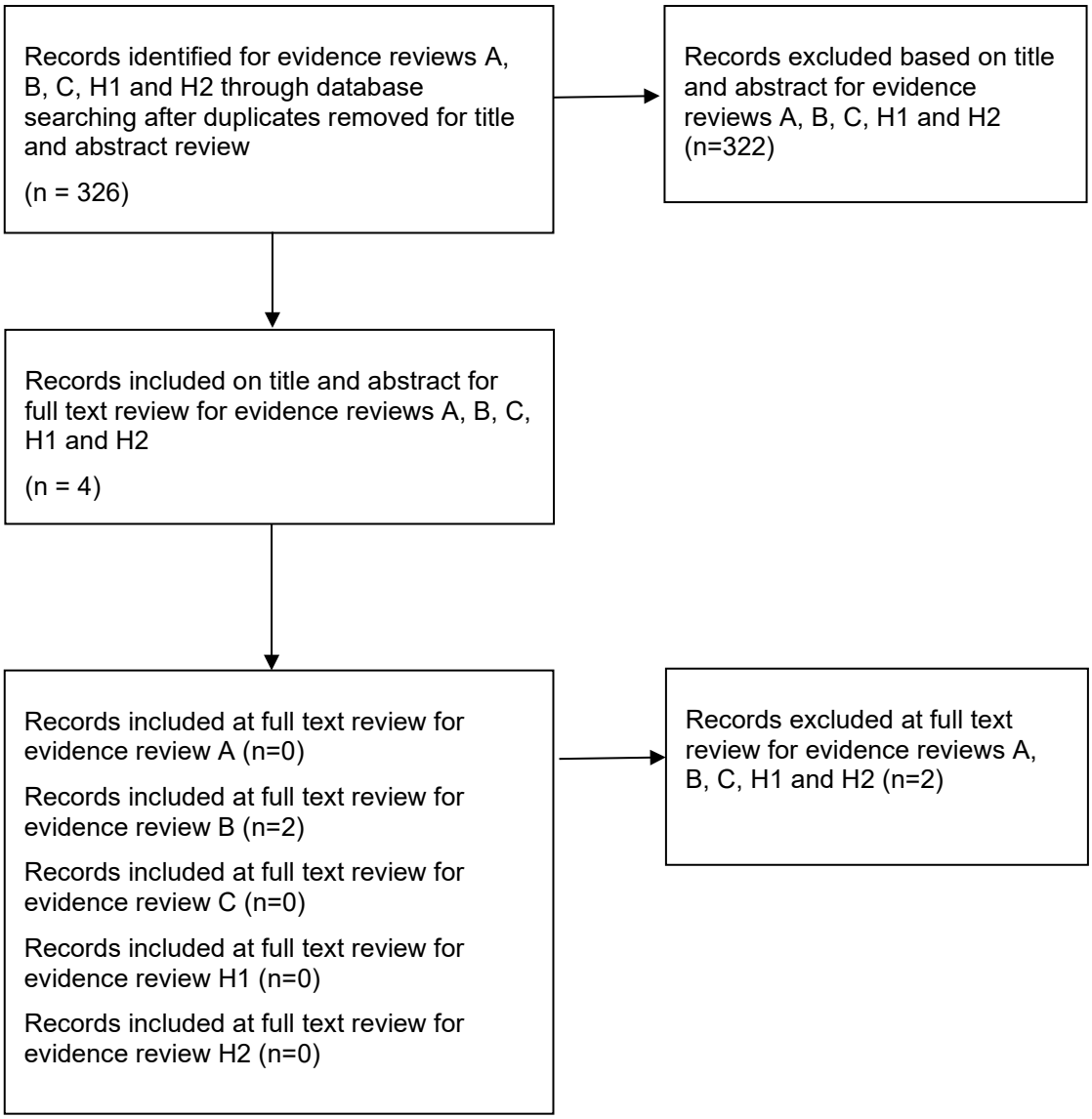
CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Downgraded twice for risk of bias. Greater than 50% of the weight in meta-analysis came from studies at high risk of bias
b. Downgraded once for inconsistency. Analysis included a single study
c. Downgraded once for imprecision. 95% confidence interval for the effect size crossed the line of no effect
d. Downgraded once for imprecision. Result comes from a study with a small sample size (sample size <576 participants)

Appendix G – Economic evidence study selection

Figure 20: Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was identified for review questions H1 and H2.

Appendix I – Health economic model

No original economic modelling was conducted for this review question.

Appendix J – Excluded studies

Effectiveness evidence excluded at full text (n=147)

Study	Reason
Abdel Raheem, Ali, Chang, Ki Don, Alenzi, Mohammed Jayed et al. (2019) Robot-Assisted Partial Nephrectomy for Totally Endophytic Renal Tumors: Step by Step Standardized Surgical Technique and Long-Term Outcomes with a Median 59-Month Follow-Up. Journal of laparoendoscopic & advanced surgical techniques. Part A 29(1): 1-11	- Exclude review C- Study included only patients T1-T2
Abdollah, Firas, Sun, Maxine, Thuret, Rodolphe et al. (2011) Mortality and morbidity after cytoreductive nephrectomy for metastatic renal cell carcinoma: a population-based study. Annals of surgical oncology 18(10): 2988-96	- Comparator in study does not match that specified in protocol *Compares radical nephrectomy Vs. cytoreductive nephrectomy. Unclear about the use of SACT*
Abedali, Zain A, Monn, M Francesca, Huddleston, Patrick et al. (2020) Robotic and open partial nephrectomy for intermediate and high complexity tumors: a matched-pairs comparison of surgical outcomes at a single institution. Scandinavian journal of urology 54(4): 313-317	- Exclude - For review C. Proportion of patients stage T3 < 90%
Abu-Ghanem, Yasmin, Fernandez-Pello, Sergio, Bex, Axel et al. (2020) Limitations of Available Studies Prevent Reliable Comparison Between Tumour Ablation and Partial Nephrectomy for Patients with Localised Renal Masses: A Systematic Review from the European Association of Urology Renal Cell Cancer Guideline Panel. European urology oncology 3(4): 433-452	- Data not reported in an extractable format
Abu-Ghanem, Yasmin, van Thienen, Johannes V, Blank, Christian et al. (2022) Cytoreductive nephrectomy and exposure to sunitinib - a post hoc analysis of the Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME) trial. BJU international 130(1): 68-75	- Study does not contain a relevant outcome *No additional outcomes to reported*
Acosta Ruiz, Vanessa, Ladjevardi, Sam, Brekkan, Einar et al. (2019) Periprocedural outcome after laparoscopic partial nephrectomy versus radiofrequency ablation for T1 renal tumors: a modified R.E.N.A.L nephrometry score adjusted comparison. Acta radiologica (Stockholm, Sweden : 1987) 60(2): 260-268	- Study published before included SR/s for the outcome/s reported

Study	Reason
Aeppli, S., Engeler, D.S., Fischer, S. et al. (2022) Incidence and outcome of patients with renal cell carcinoma treated with partial or radical nephrectomy in the Cantons St Gallen and Appenzell 2009-2018. Swiss Medical Weekly 152(2324): w30175	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Ahn, Thomas, Ellis, Robert J, White, Victoria M et al. (2018) Predictors of new-onset chronic kidney disease in patients managed surgically for T1a renal cell carcinoma: An Australian population-based analysis. Journal of surgical oncology 117(7): 1597-1610	- Primary study covered fully by an included systematic review
Alasker, Ahmed, Alnafisah, Turki Rashed, Alghafees, Mohammad et al. (2023) Preserving Renal Function without Compromising Oncological Outcomes: A Comparative Study of Partial and Total Nephrectomies in T3 Stage Renal Cell Carcinoma. Journal of kidney cancer and VHL 10(4): 28-32	- Comparator in study does not match that specified in protocol *Compared PN vs RN in T3a RCC: not relevant for review C*
Ali, Muhammad, Kwon, Young Suk, Koo, Kendrick et al. (2025) Salvage stereotactic ablative body radiotherapy after thermal ablation of primary kidney cancer. BJU international 135(1): 110-116	- Study did not compare the interventions of interest
Alnimer, Yanal, Qasrawi, Ayman, Yan, Donglin et al. (2021) Prognostic Impact of Cytoreductive Nephrectomy in Patients with Metastatic Renal Cell Carcinoma: Data from a Large Population-Based Database. Urology journal 19(2): 111-119	- Exclude - Outcome was measured using a measure out of scope
Alper, Isik and Yuksel, Esra (2016) Comparison of Acute and Chronic Pain after Open Nephrectomy versus Laparoscopic Nephrectomy: A Prospective Clinical Trial. Medicine 95(16): e3433	- There is no information on cT or pT stage
Alshyarba, M.H.M., Alamri, A., Assiri, J.M.M. et al. (2020) Treatment and overall survival in renal cell carcinoma. Bahrain Medical Bulletin 42(2): 113-115	- Data not reported in an extractable format *Kaplan-Meier for overall survival*
Althaus, Adam B, Chang, Peter, Mao, Jialin et al. (2020) Patient-Reported Quality of Life and Convalescence After Minimally Invasive Kidney Cancer Surgery. Urology 144: 123-129	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Alvim, Ricardo, Tin, Amy, Nogueira, Lucas et al. (2021) A comparison of oncologic and functional	- Comparator in study does not match that specified in protocol

Study	Reason
outcomes in patients with pt3a renal cell carcinoma treated with partial and radical nephrectomy. International braz j urol : official journal of the Brazilian Society of Urology 47(4): 777-783	*Compared RN with PN in T3a tumours - not relevant for review C.*
Alzamzami, M, Geirbely, A, Ahmed, MB et al. (2023) A Literature Review of Perioperative Outcomes of Robotic Radical Nephrectomy (RRN) Versus Laparoscopic Radical Nephrectomy (LRN) for Renal Cell Carcinoma (RCC). Cureus 15(11): e49077	- Exclude - For review C. Proportion of patients stage T3 < 90%
Amin, C., Wallen, E., Pruthi, R.S. et al. (2008) Preoperative Tyrosine Kinase Inhibition as an Adjunct to Debulking Nephrectomy. Urology 72(4): 864-868	- Study does not contain a relevant intervention *Irrelevant nephrectomy type. Study observes the patients undergone laparoscopic and radical nephrectomy*
Andrade, Hiury S, Zargar, Homayoun, Akca, Oktay et al. (2017) Is Robotic Partial Nephrectomy Safe for T3a Renal Cell Carcinoma? Experience of a High-Volume Center. Journal of endourology 31(2): 153-157	- Comparator in study does not match that specified in protocol *Compares RN and PN in T3a RCC - not relevant for review C.*
Andrews, Jack R, Lohse, Christine M, Boorjian, Stephen A et al. (2022) Outcomes following cytoreductive nephrectomy without immediate postoperative systemic therapy for patients with synchronous metastatic renal cell carcinoma. Urologic oncology 40(4): 166e1-166e8	- Comparator in study does not match that specified in protocol *None of the participants had SACT*
Anele, Uzoma A, Marchioni, Michele, Yang, Bo et al. (2019) Robotic versus laparoscopic radical nephrectomy: a large multi-institutional analysis (ROSULA Collaborative Group). World journal of urology 37(11): 2439-2450	- Exclude - For review C. Proportion of patients stage T3 < 90%
Ansari, Jawaher, Farrag, Ashraf, Ali, Arwa et al. (2021) Concurrent use of nivolumab and radiotherapy for patients with metastatic non-small cell lung cancer and renal cell carcinoma with oligometastatic disease progression on nivolumab. Molecular and clinical oncology 15(4): 214	- Study does not contain a relevant outcome
Antonelli, Alessandro, Palumbo, Carlotta, Sandri, Marco et al. (2020) Renal Function Impairment Below Safety Limits Correlates With Cancer-specific Mortality in Localized Renal Cell Carcinoma: Results From a Single-center Study. Clinical genitourinary cancer 18(4): e360-e367	- Study does not contain a relevant outcome

Study	Reason
Antonelli, Alessandro, Veccia, Alessandro, Pavan, Nicola et al. (2019) Outcomes of Partial and Radical Nephrectomy in Octogenarians - A Multicenter International Study (Resurge). Urology 129: 139-145	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Aron, Monish, Koenig, Phillipe, Kaouk, Jihad H et al. (2008) Robotic and laparoscopic partial nephrectomy: a matched-pair comparison from a high-volume centre. BJU international 102(1): 86-92	- There is no information on cT or pT stage
Artsitas, Sotirios, Artsitas, Dimitrios, Segkou, Ioanna et al. (2022) Considering "Trifecta" as a Single Outcome when Comparing Robotic With Open Partial Nephrectomy: A Mathematical Model of Volume Conservation and Systematic Review. In vivo (Athens, Greece) 36(6): 2558-2578	- Exclude - assessed outcome is out of scope
Bacic, Janine, Liu, Tao, Thompson, R Houston et al. (2020) Emulating Target Clinical Trials of Radical Nephrectomy With or Without Lymph Node Dissection for Renal Cell Carcinoma. Urology 140: 98-106	- Comparator in study does not match that specified in protocol *LND vs no LND*
Badrigilan, S., Meola, A., Chang, S.D. et al. (2023) Stereotactic radiosurgery with immune checkpoint inhibitors for brain metastases: a meta-analysis study. British Journal of Neurosurgery 37(6): 1533-1543	- Exclude - wrong population
Baio, Raffaele, Molisso, Giovanni, Caruana, Christian et al. (2023) "Could Patient Age and Gender, along with Mass Size, Be Predictive Factors for Benign Kidney Tumors?": A Retrospective Analysis of 307 Consecutive Single Renal Masses Treated with Partial or Radical Nephrectomy. Bioengineering (Basel, Switzerland) 10(7)	- Study does not contain a relevant outcome
Bamias, Aristotle, Tzannis, Kimon, Papatsoris, Athanasios et al. (2014) Prognostic significance of cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma treated with first-line sunitinib: a European multiinstitutional study. Clinical genitourinary cancer 12(5): 373-83	- Mixed population of SACT pre/post non-pharmacological regimens *No information available to interpret if the SACT was given before or after CN*
Baudo, A., Incesu, R.-B., Morra, S. et al. (2023) Other-Cause Mortality, According to Partial vs. Radical Nephrectomy: Age and Stage Analyses. Clinical Genitourinary Cancer	- Study does not contain a relevant outcome

Study	Reason
Bayrak, Omer, Seckiner, Ilker, Erturhan, Sakip et al. (2014) Comparison of the complications and the cost of open and laparoscopic radical nephrectomy in renal tumors larger than 7 centimeters. Urology journal 11(1): 1222-7	- Exclude - For review C. Proportion of patients stage T3 < 90%
Bazzi, Wassim M, Sjoberg, Daniel D, Feuerstein, Michael A et al. (2015) Long-term survival rates after resection for locally advanced kidney cancer: Memorial Sloan Kettering Cancer Center 1989 to 2012 experience. The Journal of urology 193(6): 1911-6	- Comparator in study does not match that specified in protocol
Bekema, Hendrika J, MacLennan, Steven, Imamura, Mari et al. (2013) Systematic review of adrenalectomy and lymph node dissection in locally advanced renal cell carcinoma. European urology 64(5): 799-810	- Comparator in study does not match that specified in protocol
Beksac, Alp T, Okhawere, Kennedy E, Abou Zeinab, Mahmoud et al. (2022) Robotic partial nephrectomy for management of renal mass in patients with a solitary kidney: can we expand the indication to T2 and T3 disease?. Minerva urology and nephrology 74(2): 203-208	- Exclude - For review C. Proportion of patients stage T3 < 90%
Benichou, Ygal, Audenet, Francois, Bensalah, Karim et al. (2023) Partial nephrectomy in solitary kidneys: comparison between open surgery and robotic-assisted laparoscopy on perioperative and functional outcomes (UroCCR-54 study). World journal of urology 41(2): 315-324	- Exclude - For review C. Proportion of patients stage T3 < 90%
Bianchi, Lorenzo, Chessa, Francesco, Piazza, Pietro et al. (2022) Percutaneous ablation or minimally invasive partial nephrectomy for cT1a renal masses? A propensity score-matched analysis. International journal of urology : official journal of the Japanese Urological Association 29(3): 222-228	- Secondary publication of an included study that does not provide any additional relevant information
Binsaleh, Saleh, Madbouly, Khaled, Matsumoto, Edward D et al. (2015) A Prospective Randomized Study of Pfannenstiel Versus Expanded Port Site Incision for Intact Specimen Extraction in Laparoscopic Radical Nephrectomy. Journal of endourology 29(8): 913-8	- Exclude - Intervention is out of scope
Blom, Jan H M, van Poppel, Hein, Marechal, Jean M et al. (2009) Radical nephrectomy with	- Comparator in study does not match that specified in protocol

Study	Reason
and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. European urology 55(1): 28-34	*Lymphadenectomy vs no lymphadenectomy*
Bosse, Dominick, Lin, Xun, Simantov, Ronit et al. (2019) Response of Primary Renal Cell Carcinoma to Systemic Therapy. European urology 76(6): 852-860	- Not a relevant study design *Pooled Analysis*
Boylu, U., Basatac, C., Yildirim, U. et al. (2015) Comparison of surgical, functional, and oncological outcomes of open and robot-assisted partial nephrectomy. Journal of Minimal Access Surgery 11(1): 72-77	- Exclude - For review C. Proportion of patients stage T3 < 90%
Bravi, C.A., on behalf of the Junior ERUS/Young Academic Urologist Working Group on Robot-Assisted, Surgery, Dell'Oglio, P. et al. (2024) Surgical Experience and Functional Outcomes after Laparoscopic and Robot-Assisted Partial Nephrectomy: Results from a Multi-Institutional Collaboration. Journal of Clinical Medicine 13(19): 6016	- Exclude - review C. Patients with localised tumour
Breda, Alberto; Anterasian, Christine; Belldegrun, Arie (2010) Management and outcomes of tumor recurrence after focal ablation renal therapy. Journal of endourology 24(5): 749-52	- More recent systematic review included that covers the same topic
Britton, Cameron J, Sharma, Vidit, Lohse, Christine M et al. (2022) Progression of Chronic Kidney Disease Following Radical and Partial Nephrectomy. Urology 169: 125-133	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Brown, Janet E, Royle, Kara-Louise, Gregory, Walter et al. (2023) Temporary treatment cessation versus continuation of first-line tyrosine kinase inhibitor in patients with advanced clear cell renal cell carcinoma (STAR): an open-label, non-inferiority, randomised, controlled, phase 2/3 trial. The Lancet. Oncology 24(3): 213-227	- Study does not contain a relevant intervention
Buckland, Benjamin, Tree, Kevin, Best, Oliver et al. (2024) Robotic versus Laparoscopic Partial Nephrectomy: A Systematic Review and Meta-Analysis of Randomised Trials. Surgical technology international 45	- Exclude - review C. Patients with localised tumour

Study	Reason
Burgess, Neil A, Koo, Brendan C, Calvert, Robert C et al. (2007) Randomized trial of laparoscopic v open nephrectomy. Journal of endourology 21(6): 610-3	- There is no information on cT or pT stage
Cacciamani, Giovanni E, Medina, Luis G, Gill, Tania et al. (2018) Impact of Surgical Factors on Robotic Partial Nephrectomy Outcomes: Comprehensive Systematic Review and Meta-Analysis. The Journal of urology 200(2): 258-274	- Exclude - For review C. Proportion of patients stage T3 < 90%
Cai, Yi; Li, Han-Zhong; Zhang, Yu-Shi (2018) Comparison of Partial and Radical Laparascopic Nephrectomy: Long-Term Outcomes for Clinical T1b Renal Cell Carcinoma. Urology journal 15(2): 16-20	- Non-OECD country
Calpin, Gavin G, Ryan, Fintan R, McHugh, Fiachra T et al. (2023) Comparing the outcomes of open, laparoscopic and robot-assisted partial nephrectomy: a network meta-analysis. BJU international 132(4): 353-364	- Exclude - For C. Proportion of patients stage T3 < 90%
Calpin, GG, Ryan, FR, McHugh, FT et al. (2023) Comparing the Outcomes of Open, Laparoscopic & Robotic Partial Nephrectomy: A Network Meta-Analysis. BJU international	- Duplicate reference
Campi, Riccardo, Berni, Alessandro, Amparore, Daniele et al. (2022) Impact of frailty on perioperative and oncologic outcomes in patients undergoing surgery or ablation for renal cancer: a systematic review. Minerva urology and nephrology 74(2): 146-160	- More recent systematic review included that covers the same topic
Cao, Dalong, Huang, Yongqiang, Zhang, Chuankai et al. (2019) Adverse Effect of Lymph Node Dissection in Metastatic Renal Cell Cancer Patients Treated with Cytoreductive Nephrectomy: A Contemporary Analysis of Survival. Journal of Cancer 10(19): 4639-4646	- Study did not compare the interventions of interest
Capitanio, U., Larcher, A., Cianflone, F. et al. (2020) Hypertension and Cardiovascular Morbidity Following Surgery for Kidney Cancer. European Urology Oncology 3(2): 209-215	- Primary study covered fully by an included systematic review
Capitanio, Umberto, Zini, Laurent, Perrotte, Paul et al. (2008) Cytoreductive partial nephrectomy does not undermine cancer control in metastatic renal cell carcinoma: a population-based study. Urology 72(5): 1090-5	- Study does not contain a relevant intervention *Compares partial nephrectomy with radical nephrectomy*

Study	Reason
Carvalho, Filipe L F, Zheng, Chaoyi, Witmer, Kenneth et al. (2019) Complications associated with perioperative use of tyrosine kinase inhibitor in cytoreductive nephrectomy. Scientific reports 9(1): 15272	- Study does not contain a relevant intervention *Compares nephrectomy followed by SACT vs. nephrectomy alone.* *- study evaluates the effect of preoperative SACT. It's unclear whether SACT was given before or after the surgery.*
Castilho, Tiago Mendonca Lopez, Lemos, Gustavo Caserta, Cha, Jonathan Doyun et al. (2020) Transition from open partial nephrectomy directly to robotic surgery: experience of a single surgeon to achieve "TRIFECTA". International braz j urol : official journal of the Brazilian Society of Urology 46(5): 814-821	- Exclude - Study with a single arm
Cerrato, Clara, Meagher, Margaret F, Autorino, Riccardo et al. (2023) Partial versus radical nephrectomy for complex renal mass: multicenter comparative analysis of functional outcomes (Rosula collaborative group). Minerva urology and nephrology 75(4): 425-433	- Study does not contain a relevant outcome *Outcomes presented for T1, T2 and T3 combined*
Chan, Vinson Wai-Shun, Tan, Wei Shen, Leow, Jeffrey J et al. (2021) Delayed surgery for localised and metastatic renal cell carcinoma: a systematic review and meta-analysis for the COVID-19 pandemic. World journal of urology 39(12): 4295-4303	- Exclude - Result reported in the most updated MA
Chanbour, Hani, Chen, Jeffrey W, Bendfeldt, Gabriel A et al. (2024) Impact of Targeted Systemic Therapy and Radiotherapy on Patients Undergoing Spine Surgery for Metastatic Renal Cell Carcinoma. International journal of spine surgery 18(3): 343-352	- Exclude - Intervention is out of scope *Spinal surgery*
Chang, Ki Don, Abdel Raheem, Ali, Kim, Kwang Hyun et al. (2018) Functional and oncological outcomes of open, laparoscopic and robot-assisted partial nephrectomy: a multicentre comparative matched-pair analyses with a median of 5 years' follow-up. BJU international 122(4): 618-626	- Exclude review C - Study included only patients T1-T2
Chang, Xiaofeng, Liu, Tieshi, Zhang, Fan et al. (2015) Radiofrequency ablation versus partial nephrectomy for clinical T1a renal-cell carcinoma: long-term clinical and oncologic outcomes based on a propensity score analysis. Journal of endourology 29(5): 518-25	- Non-OECD country
Chang, Xiaofeng, Zhang, Fan, Liu, Tieshi et al. (2015) Radio frequency ablation versus partial	- Non-OECD country

Study	Reason
nephrectomy for clinical T1b renal cell carcinoma: long-term clinical and oncologic outcomes. The Journal of urology 193(2): 430-5	
Chang, Ying-Hsu, Chang, Su-Wei, Liu, Chung-Yi et al. (2018) Demographic characteristics and complications of open and minimally invasive surgeries for renal cell carcinoma: a population-based case-control study in Taiwan. Therapeutics and clinical risk management 14: 1235-1241	- Non-OECD country
Chapin, Brian F, Delacroix, Scott E Jr, Culp, Stephen H et al. (2011) Safety of presurgical targeted therapy in the setting of metastatic renal cell carcinoma. European urology 60(5): 964-71	- Comparator in study does not match that specified in protocol *Study compares SACT followed by CN with immediate CN. Results section indicates that both groups received SACT post surgery as well.*
Chapman, Terence N, Sharma, Satish, Zhang, Shaozeng et al. (2008) Laparoscopic lymph node dissection in clinically node-negative patients undergoing laparoscopic nephrectomy for renal carcinoma. Urology 71(2): 287-91	- Comparator in study does not match that specified in protocol *LND vs no LND*
Chen, Bo, Li, Jinze, Huang, Yin et al. (2023) The role of cytoreductive nephrectomy in metastatic renal cell carcinoma in the targeted therapy and immunological therapy era: a systematic review and meta-analysis. International journal of surgery (London, England) 109(4): 982-994	- Exclude - error in the paper
Chen, Yonghui, Wu, Xiaorong, Zhou, Jiale et al. (2022) Thermal ablation assisted laparoscopic partial nephrectomy for clinical T1b renal tumors. Minimally invasive therapy & allied technologies : MITAT : official journal of the Society for Minimally Invasive Therapy 31(2): 179-184	- Non-OECD country
Cheung, Douglas C and Finelli, Antonio (2017) Active Surveillance in Small Renal Masses in the Elderly: A Literature Review. European urology focus 3(45): 340-351	- More recent systematic review included that covers the same topic
Cheung, Patrick, Patel, Samir, North, Scott A et al. (2021) Stereotactic Radiotherapy for Oligoprogression in Metastatic Renal Cell Cancer Patients Receiving Tyrosine Kinase Inhibitor Therapy: A Phase 2 Prospective Multicenter Study. European urology 80(6): 693-700	- Not a relevant study design

Study	Reason
Chiancone, Francesco, Fabiano, Marco, Meccariello, Clemente et al. (2021) Laparoscopic versus open partial nephrectomy for the management of highly complex renal tumors with PADUA score 10: A single center analysis. Urologia 88(4): 343-347	- Exclude review C- Study included only patients T1-T2
Chiou, Jiun-Kai, Chang, Li-Wen, Li, Jian-Ri et al. (2023) Metastasectomy Improves Overall Survival in Metastatic Renal Cell Carcinoma: A Retrospective Cohort Study. Anticancer research 43(7): 3193-3201	- Mixed population of SACT pre/post non-pharmacological regimens *All participants received SACT. Not sufficient information to know the timeline of SACT.Compares patients undergone metastasectomy vs. non-metastasectomy.*
Chlorogiannis, David-Dimitris, Kratiras, Zisis, Efthymiou, Evgenia et al. (2024) Percutaneous Microwave Ablation Versus Robot-Assisted Partial Nephrectomy for Stage I Renal Cell Carcinoma: A Propensity-Matched Cohort Study Focusing Upon Long-Term Follow-Up of Oncologic Outcomes. Cardiovascular and interventional radiology 47(5): 573-582	- Data not reported in an extractable format
Cho, C L, Ho, K L, Chu, S S M et al. (2011) Robot-assisted versus standard laparoscopic partial nephrectomy: comparison of perioperative outcomes from a single institution. Hong Kong medical journal = Xianggang yi xue za zhi 17(1): 33-8	- Non-OECD country - Not a relevant study design *Consecutive case series*
Choi, Chang Il, Kang, Minyong, Sung, Hyun Hwan et al. (2018) Oncologic Outcomes of Cytoreductive Nephrectomy in Synchronous Metastatic Renal-Cell Carcinoma: A Single-Center Experience. Clinical genitourinary cancer 16(6): e1189-e1199	- Mixed population of SACT pre/post non-pharmacological regimens *All participants received SACT. Not sufficient information to know the timeline of SACT.*
Choi, J.D., Park, J.W., Lee, H.W. et al. (2013) A comparison of surgical and functional outcomes of robot-assisted versus pure laparoscopic partial nephrectomy. Journal of the Society of Laparoendoscopic Surgeons 17(2): 292-299	- Exclude review C. Study included only patients T1-T2
Choi, J.E., You, J.H., Kim, D.K. et al. (2015) Comparison of perioperative outcomes between robotic and laparoscopic partial nephrectomy: A systematic review and meta-analysis. European Urology 67(5): 891-901	- Exclude - review C. Patients with localised tumour
Choi, Se Young, Ha, Moon Soo, Lee, Jeong Woo et al. (2023) Shifting role of cytoreductive nephrectomy according to type of systemic	- Mixed population of SACT pre/post non-pharmacological regimens *All participants received SACT. Not sufficient information to know the timeline of SACT.*

Study	Reason
therapy: A nationwide cohort study. Asian journal of surgery 46(1): 328-336	
Choi, Se Young, Jung, Han, You, Dalsan et al. (2019) Robot-assisted partial nephrectomy is associated with early recovery of renal function: Comparison of open, laparoscopic, and robot-assisted partial nephrectomy using DTPA renal scintigraphy. Journal of surgical oncology 119(7): 1016-1023	- There is no information on cT or pT stage
Chung, Doo Yong, Kang, Dong Hyuk, Kim, Jong Won et al. (2020) Comparison of oncologic outcomes between partial nephrectomy and radical nephrectomy in patients who were upstaged from cT1 renal tumor to pT3a renal cell carcinoma: an updated systematic review and meta-analysis. Therapeutic advances in urology 12: 1756287220981508	- Comparator in study does not match that specified in protocol *PN vs RN for upstaged pT3 tumour*
Chung, Jae-Seung, Son, Nak Hoon, Lee, Sang Eun et al. (2018) Partial versus Radical Nephrectomy for T1-T2 Renal Cell Carcinoma in Patients with Chronic Kidney Disease Stage III: a Multiinstitutional Analysis of Kidney Function and Survival Rate. Journal of Korean medical science 33(43): e277	- More recent systematic review included that covers the same topic *already included by Ochoa but also reports HR in people with CKD 30 ≤ eGFR < 60 in table 2 Looks like Ochoa only included new onset CKD which is why they've only used the stage i-iii values - can exclude*
Cinar, O., Bolat, M.S., Cicek, M.C. et al. (2020) Experiences of Laparoscopic Partial Nephrectomy for T1a Kidney Tumours: Results of Two Hundred and Fifteen Patients. Bulletin of Urooncology 19(3): 130-135	- Exclude - review C. Study included only patients T1-T2
Colombo, Jose R Jr, Haber, Georges-Pascal, Jelovsek, John E et al. (2008) Seven years after laparoscopic radical nephrectomy: oncologic and renal functional outcomes. Urology 71(6): 1149-54	- Exclude - For review C. Proportion of patients stage T3 < 90%
Correa, Rohann J M, Louie, Alexander V, Zaorsky, Nicholas G et al. (2019) The Emerging Role of Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. European urology focus 5(6): 958-969	- More recent systematic review included that covers the same topic
Cotta, Brittney H, Meagher, Margaret F, Patil, Dattatraya et al. (2021) Elevated preoperative C-reactive protein is associated with renal functional decline and non-cancer mortality in surgically treated renal cell carcinoma: analysis from the INternational Marker Consortium for	- Primary study covered fully by an included systematic review

Study	Reason
Renal Cancer (INMARC). BJU international 127(3): 311-317	
Crocerossa, Fabio, Autorino, Riccardo, Derweesh, Ithaar et al. (2023) Management of renal cell carcinoma in transplant kidney: a systematic review and meta-analysis. Minerva urology and nephrology 75(1): 1-16	- Does not contain a population of people with kidney cancer *Transplanted kidneys only*
Crocerossa, Fabio, Carbonara, Umberto, Cantiello, Francesco et al. (2021) Robot-assisted Radical Nephrectomy: A Systematic Review and Meta-analysis of Comparative Studies. European urology 80(4): 428-439	- Exclude - For review C. Proportion of patients stage T3 < 90%
Culp, Stephen H, Tannir, Nizar M, Abel, E Jason et al. (2010) Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy?. Cancer 116(14): 3378-88	- Mixed population of SACT pre/post non-pharmacological regimens *All participants received SACT. Not sufficient information to know the timeline of SACT received before or after CN.*
Dabestani, Saeed, Marconi, Lorenzo, Hofmann, Fabian et al. (2014) Local treatments for metastases of renal cell carcinoma: a systematic review. The Lancet. Oncology 15(12): e549-61	- Mixed population of SACT pre/post non-pharmacological regimens
Dahm, P., Ergun, O., Uhlig, A. et al. (2024) Cytoreductive nephrectomy in metastatic renal cell carcinoma. Cochrane Database of Systematic Reviews 2024(6): cd013773	- Systematic review used as source of primary studies
Dahm, Philipp, Ergun, Onuralp, Uhlig, Annemarie et al. (2024) Cytoreductive nephrectomy in metastatic renal cell carcinoma. The Cochrane database of systematic reviews 6: cd013773	- Duplicate reference
Danzig, Matthew R, Ghandour, Rashed A, Chang, Peter et al. (2015) Active Surveillance is Superior to Radical Nephrectomy and Equivalent to Partial Nephrectomy for Preserving Renal Function in Patients with Small Renal Masses: Results from the DISSRM Registry. The Journal of urology 194(4): 903-9	- Primary study covered fully by an included systematic review
Dariane, Charles; Timsit, Marc-Olivier; Mejean, Arnaud (2018) Position of cytoreductive nephrectomy in the setting of metastatic renal cell carcinoma patients: does the CARMENA trial lead to a paradigm shift?. Bulletin du cancer 105suppl3: 229-s234	- Systematic review used as source of primary studies

Study	Reason
Das, Manoj K, Rohith, Gorrepati, Mandal, Swarnendu et al. (2024) Intraoperative ultrasonography (IOUS)-guided vs conventional laparoscopic nephrectomy: a randomised control trial. BJU international 133(1): 71-78	- Exclude - Intervention is out of scope
Dash, A., Vickers, A.J., Schachter, L.R. et al. (2006) Comparison of outcomes in elective partial vs radical nephrectomy for clear cell renal cell carcinoma of 4-7 cm. BJU International 97(5): 939-945	- For review A. Study published before 2016 (search date for disease-free survival)
de Bruijn, Roderick, Wimalasingham, Akhila, Szabados, Bernadett et al. (2020) Deferred Cytoreductive Nephrectomy Following Presurgical Vascular Endothelial Growth Factor Receptor-targeted Therapy in Patients with Primary Metastatic Clear Cell Renal Cell Carcinoma: A Pooled Analysis of Prospective Trial Data. European urology oncology 3(2): 168-173	- Systematic review used as source of primary studies
De Gobbi, Alberto, Biasoni, Davide, Catanzaro, Mario et al. (2018) Surgery of locally advanced and metastatic kidney cancer after tyrosine kinase inhibitors therapy: single institute experience. Tumori 104(5): 388-393	- Not a relevant study design *observational study*
de Saint Aubert, N, Audenet, F, Mccaig, F et al. (2018) Nephron sparing surgery in tumours greater than 7cm. Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie 28(6): 336-343	- Primary study covered fully by an included systematic review
Deka, H., Medam, N.M., Ginil Kumar, P. et al. (2024) Comparison of Trifecta and Pentafecta Outcomes across 3 Surgical Modalities of Partial Nephrectomy (PN) - Open, Lap, and Robotic. Journal of Kidney Cancer and VHL 11(3): 27	- Exclude - For review C. Proportion of patients stage T3 < 90%
Deng, Huan, Fan, Yan, Yuan, Feifei et al. (2021) Partial nephrectomy provides equivalent oncologic outcomes and better renal function preservation than radical nephrectomy for pathological T3a renal cell carcinoma: A meta-analysis. International braz j urol : official journal of the Brazilian Society of Urology 47(1): 46-60	- Comparator in study does not match that specified in protocol *Compares RN vs PN for T3 tumours*
Deng, Wen, Chen, Luyao, Wang, Yibing et al. (2019) Cryoablation versus Partial Nephrectomy for Clinical Stage T1 Renal Masses: A Systematic Review and Meta-Analysis. Journal of Cancer 10(5): 1226-1236	- More recent systematic review included that covers the same topic

Study	Reason
Deng, Wen, Zhou, Zhengtao, Zhong, Jian et al. (2020) Retroperitoneal laparoscopic partial versus radical nephrectomy for large (>= 4 cm) and anatomically complex renal tumors: A propensity score matching study. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 46(7): 1360-1365	- Non-OECD country
Dengina, N., Mitin, T., Gamayunov, S. et al. (2019) Stereotactic body radiation therapy in combination with systemic therapy for metastatic renal cell carcinoma: A prospective multicentre study. ESMO Open 4(5): e000535	- Not a relevant study design
Desideri, I, Francolini, G, Scotti, V et al. (2019) Benefit of ablative versus palliative-only radiotherapy in combination with nivolumab in patients affected by metastatic kidney and lung cancer. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico 21(7): 933-938	- Does not contain a population of people with kidney cancer *Mix of non-small cell lung cancer and RCC. No separate results for participants with RCC reported.No comparator groupParticipants received RT and SACT simultaneously. Or RT given at least 60 days after the last does of SACT.*
Dillenburg, Wolfgang, Poulakis, Vassilis, Skriapas, Konstantinos et al. (2006) Retroperitoneoscopic versus open surgical radical nephrectomy for large renal cell carcinoma in clinical stage cT2 or cT3a: quality of life, pain and reconvalescence. European urology 49(2): 314-3	- Exclude - For review C. Proportion of patients stage T3 < 90%
Dong, Bao Nan, Song, Jie, Yang, Wen Li et al. (2024) Comparison of Outcomes Between Partial and Radical Laparoscopic Nephrectomy for Localized Renal Tumors Larger Than Four Centimeters: A Systematic Review and Meta-Analysis. World journal of oncology 15(4): 625-639	- Systematic review with case control studies
Dong, Hanzhi, Cao, Yuan, Jian, Yan et al. (2023) Patients with metastatic renal cell carcinoma who receive immune-targeted therapy may derive survival benefit from nephrectomy. BMC cancer 23(1): 943	- Study does not contain a relevant intervention *Compares SACT vs. non pharma (nephrectomy). Only 40% of the patients in the nephrectomy arm underwent CN with rest of them arm receiving radical nephrectomy. No subgroup data available.*
Dong, Lin, Liang, Wang You, Ya, Lu et al. (2022) A Systematic Review and Meta-Analysis of Minimally Invasive Partial Nephrectomy Versus Focal Therapy for Small Renal Masses. Frontiers in oncology 12: 732714	- Does not contain a population of people with kidney cancer *SR focussing on small renal masses*

Study	Reason
Dragomir, Alice, Nazha, Sara, Wood, Lori A et al. (2020) Outcomes of complete metastasectomy in metastatic renal cell carcinoma patients: The Canadian Kidney Cancer information system experience. Urologic oncology 38(10): 799e1-799e10	- Study does not contain a relevant intervention *compares mastectomy Vs. no mastectomy. No information regarding the use of SACT prior or during the mastectomy is given. Baseline data reports percentage of patients used SCAT during follow-up, which can not be used to determine the timeline of SCAT*
El-Ghazaly, Tarek H; Mason, Ross J; Rendon, Ricardo A (2014) Oncological outcomes of partial nephrectomy for tumours larger than 4 cm: A systematic review. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 8(12): 61-6	- There is no information on cT or pT stage
Ellis, E.E. and Messing, E. (2021) Active Surveillance of Small Renal Masses: A Systematic Review. Kidney Cancer 5(3): 139-152	- More recent systematic review included that covers the same topic
Ellison, Jonathan S, Montgomery, Jeffrey S, Wolf, J Stuart Jr et al. (2012) A matched comparison of perioperative outcomes of a single laparoscopic surgeon versus a multisurgeon robot-assisted cohort for partial nephrectomy. The Journal of urology 188(1): 45-50	- Exclude - For review C. Proportion of patients stage T3 < 90%
Enikeev, Dmitry, Morozov, Andrey, Bazarkin, Andrey et al. (2023) Thermal ablation vs. active surveillance for renal masses: a systematic review and network meta-analysis. Minerva urology and nephrology 75(2): 154-162	- More recent systematic review included that covers the same topic *Reports unadjusted outcomes only*
Ergun, Muslum, Sagir, Suleyman, Akyuz, Osman et al. (2024) Evolving Approach in Nephron-Sparing Surgery: Has Anything Changed from Open Surgery to Laparoscopy?. Archivos espanoles de urologia 77(7): 726-731	- Exclude - review C. Patients with localised tumour
Faddegon, Stephen, Ju, Tom, Olweny, Ephrem O et al. (2013) A comparison of long term renal functional outcomes following partial nephrectomy and radiofrequency ablation. The Canadian journal of urology 20(3): 6785-9	- Study published before included SR/s for the outcome/s reported
Faiena, Izak, Salmasi, Amirali, Lenis, Andrew T et al. (2018) Overall survival in patients with metastatic renal cell carcinoma and clinical N1 disease undergoing cytoreductive nephrectomy and lymph node dissection. Urologic oncology 36(2): 79e19-79e26	- Study does not contain a relevant intervention *Compares lymphadenectomy vs. No lymphadenectomy. All had previously received CN, no information of background use of SACT given. No additional sub-group analysis*

Study	Reason
Fallah, Jaleh, Gittleman, Haley, Weinstock, Chana et al. (2024) Cytoreductive nephrectomy in the era of immune checkpoint inhibitors: a US Food and Drug Administration pooled analysis. Journal of the National Cancer Institute 116(7): 1043-1050	- Exclude - Intervention is out of scope *Pooled analysis of trials comparing pharmaceuticals only.*
Feder, Marc T, Patel, Manoj B, Melman, Arnold et al. (2008) Comparison of open and laparoscopic nephrectomy in obese and nonobese patients: outcomes stratified by body mass index. The Journal of urology 180(1): 79-83	- Exclude - For review C. Proportion of patients stage T3 < 90%
Feuerstein, Michael A, Kent, Matthew, Bazzi, Wassim M et al. (2014) Analysis of lymph node dissection in patients with >=7-cm renal tumors. World journal of urology 32(6): 1531-6	- Comparator in study does not match that specified in protocol - Study did not compare the interventions of interest
Feuerstein, Michael A, Kent, Matthew, Bernstein, Melanie et al. (2014) Lymph node dissection during cytoreductive nephrectomy: a retrospective analysis. International journal of urology : official journal of the Japanese Urological Association 21(9): 874-9	- Study does not contain a relevant intervention *Compares lymphadenectomy vs. No lymphadenectomy. All had previously received CN, no information of background use of SACT given.*
Ficarra, V., Crestani, A., Inferrera, A. et al. (2018) Positive surgical margins after partial nephrectomy: A systematic review and meta-analysis of comparative studies. Kidney Cancer 2(2): 133-145	- Exclude - assessed outcome is out of scope
Ficarra, Vincenzo, Minervini, Andrea, Antonelli, Alessandro et al. (2014) A multicentre matched-pair analysis comparing robot-assisted versus open partial nephrectomy. BJU international 113(6): 936-41	- Exclude review C Study included only patients T1-T2
Figaroa, Orlane, Zondervan, Patricia, Kessels, Rob et al. (2024) PrimerX: A Bayesian Multistage Cohort Embedded Randomised Trial to Evaluate the Role of Deferred Local Therapy of the Primary Tumour in Combination with Immune Checkpoint Inhibitor-based First-line Therapy in Metastatic Renal Cell Carcinoma Patients. European urology open science 70: 28-35	- Comparator in study does not match that specified in protocol *People in the comparator group were allowed to receive deferred CN if primary tumour was progressing*
Fossati, Nicola, Larcher, Alessandro, Gadda, Giulio M et al. (2015) Minimally Invasive Partial Nephrectomy Versus Laparoscopic Cryoablation for Patients Newly Diagnosed with a Single	- Primary study covered fully by an included systematic review

Study	Reason
Small Renal Mass. European urology focus 1(1): 66-72	
Franzese, Ciro, Marini, Beatrice, Baldaccini, Davide et al. (2023) The impact of stereotactic ablative radiotherapy on oligoprogressive metastases from renal cell carcinoma. Journal of cancer research and clinical oncology 149(8): 4411-4417	- Review H - SABR exclude *All patients received active SCAT during SABR*
Franzese, Ciro, Marvaso, Giulia, Francolini, Giulio et al. (2021) The role of stereotactic body radiation therapy and its integration with systemic therapies in metastatic kidney cancer: a multicenter study on behalf of the AIRO (Italian Association of Radiotherapy and Clinical Oncology) genitourinary study group. Clinical & experimental metastasis 38(6): 527-537	- Review H - SABR exclude
Gandi, C., Totaro, A., Bientinesi, R. et al. (2022) Purely Off-Clamp Partial Nephrectomy: Robotic Approach Better than Open Using a Pentafecta Outcome with Propensity Score Matching. Journal of Clinical Medicine 11(21): 6241	- Exclude - For review C. Proportion of patients stage T3 < 90%
Gao, HuiYu, Zhou, Lin, Zhang, JiaBin et al. (2024) Comparative efficacy of cryoablation versus robot-assisted partial nephrectomy in the treatment of cT1 renal tumors: a systematic review and meta-analysis. BMC cancer 24(1): 1150	- Systematic review used as source of primary studies
Gao, X., Hu, L., Pan, Y. et al. (2018) Surgical outcomes of nephrectomy for elderly patients with renal cell carcinoma. Pakistan Journal of Medical Sciences 34(2): 288-293	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Garcia-Perdomo, Herney A; Zapata-Copete, James A; Castillo-Cobaleda, Diego F (2018) Role of cytoreductive nephrectomy in the targeted therapy era: A systematic review and meta-analysis. Investigative and clinical urology 59(1): 2-9	- Exclude - Result reported in the most updated MA
Garg, Harshit, Das, Bhabatosh, Bansal, Amit et al. (2022) Trifecta and Pentafecta Outcomes in Laparoscopic and Robotic Nephron-Sparing Surgery for Highly Complex Renal Tumors: A Propensity Score-Matched Cohort Analysis. Journal of endourology 36(8): 1050-1056	- Exclude - review C - Study included only patients T1-T2
Garg, Harshit, Tiwari, Deviprasad, Nayak, Brusabhanu et al. (2020) A comparative	- Exclude -review C- Study included only patients T1-T2

Study	Reason
analysis of various surgical approaches of nephron-sparing surgery and correlation of histopathological grade with RENAL nephrometry score in renal cell carcinoma. Journal of minimal access surgery 16(2): 144-151	
Garisto, Juan, Bertolo, Riccardo, Dagenais, Julien et al. (2018) Robotic versus open partial nephrectomy for highly complex renal masses: Comparison of perioperative, functional, and oncological outcomes. Urologic oncology 36(10): 471e1-471e9	- Exclude -review C- Study included only patients T1-T2
Ge, Si, Wang, Zuoping, Li, Yunxiang et al. (2025) Is Ablation Suitable For Small Renal Masses? A Meta-Analysis. Academic radiology 32(1): 218-235	- Systematic review used as source of primary studies
Gebbia, Vittorio, Girlando, Andrea, DI Grazia, Alfio et al. (2020) Stereotactic Radiotherapy for the Treatment of Patients With Oligo-progressive Metastatic Renal Cell Carcinoma Receiving Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor: Data From the Real World. Anticancer research 40(12): 7037-7043	- Review H - SABR exclude *All participants received concomitant SACT*
Gershman, Boris, Moreira, Daniel M, Thompson, R Houston et al. (2018) Perioperative Morbidity of Lymph Node Dissection for Renal Cell Carcinoma: A Propensity Score-based Analysis. European urology 73(3): 469-475	- Comparator in study does not match that specified in protocol
Gershman, Boris, Thompson, R Houston, Boorjian, Stephen A et al. (2018) Radical Nephrectomy with or without Lymph Node Dissection for High Risk Nonmetastatic Renal Cell Carcinoma: A Multi-Institutional Analysis. The Journal of urology 199(5): 1143-1148	- Exclude - For review C. Proportion of patients stage T3 < 90% - Comparator in study does not match that specified in protocol *LND vs no LND*
Gershman, Boris, Thompson, R Houston, Moreira, Daniel M et al. (2017) Lymph Node Dissection is Not Associated with Improved Survival among Patients Undergoing Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma: A Propensity Score Based Analysis. The Journal of urology 197(3pt1): 574-579	- Mixed population of SACT pre/post non-pharmacological regimens - Study does not contain a relevant intervention *Compares CN with lymphadenectomy vs. CN without lymphadenectomy.Mixed population with pre and post non-pharmacological treatment.*
Gershman, Boris, Thompson, R Houston, Moreira, Daniel M et al. (2017) Radical Nephrectomy With or Without Lymph Node	- Comparator in study does not match that specified in protocol *LND vs no LND*

Study	Reason
Dissection for Nonmetastatic Renal Cell Carcinoma: A Propensity Score-based Analysis. European urology 71(4): 560-567	
Ghani, Khurshid R, Sukumar, Shyam, Sammon, Jesse D et al. (2014) Practice patterns and outcomes of open and minimally invasive partial nephrectomy since the introduction of robotic partial nephrectomy: results from the nationwide inpatient sample. The Journal of urology 191(4): 907-12	- There is no information on cT or pT stage
Gill, Inderbir S, Matin, Surena F, Desai, Mihir M et al. (2003) Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumors in 200 patients. The Journal of urology 170(1): 64-8	- Exclude - For review C. Proportion of patients stage T3 < 90%
Golombos, D.M., Chughtai, B., Trinh, Q.-D. et al. (2017) Adoption of technology and its impact on nephrectomy outcomes, a U.S. population-based analysis (2008-2012). Journal of Endourology 31(1): 91-99	- Exclude - For review C. Proportion of patients stage T3 < 90%
Golombos, David M, Chughtai, Bilal, Trinh, Quoc-Dien et al. (2017) Minimally invasive vs open nephrectomy in the modern era: does approach matter?. World journal of urology 35(10): 1557-1568	- Exclude - For review C. Proportion of patients stage T3 < 90% *Reported as stage 3*
Gonzalez-Ruiz de Leon, C., Pellejero-Perez, P., Quintas-Blanco, A. et al. (2017) Beneficio de la nefrectomia en el tratamiento del carcinoma de celulas renales metastasico, Benefit of on nephrectomy for treating metastatic renal cell carcinoma. Actas urologicas espanolas 41(5): 338-342	- Exclude - non-English paper
Graham, Jeffrey, Wells, J Connor, Donskov, Frede et al. (2019) Cytoreductive Nephrectomy in Metastatic Papillary Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. European urology oncology 2(6): 643-648	- Exclude - Result reported in the most updated MA
Green, Harshani; Taylor, Alexandra; Khoo, Vincent (2023) Beyond the Knife in Renal Cell Carcinoma: A Systematic Review-To Ablate or Not to Ablate?. Cancers 15(13)	- More recent systematic review included that covers the same topic
Grimaud, L.W., Chen, F.V., Chang, J. et al. (2021) Comparison of Perioperative Outcomes for Radical Nephrectomy Based on Surgical	- Exclude - For review C. Proportion of patients stage T3 < 90% *Study excluded cT3b-4 disease*

Study	Reason
Approach for Masses Greater Than 10 cm. Journal of Endourology 35(12): 1785-1792	
Grimm, Marc-Oliver, Oya, Mototsugu, Choueiri, Toni K et al. (2024) Impact of Prior Cytoreductive Nephrectomy on Efficacy in Patients with Synchronous Metastatic Renal Cell Carcinoma Treated with Avelumab plus Axitinib or Sunitinib: Post Hoc Analysis from the JAVELIN Renal 101 Phase 3 Trial. European urology 85(1): 8-12	- Not a relevant study design
Grivas, Nikolaos, Kalampokis, Nikolaos, Larcher, Alessandro et al. (2019) Robot-assisted versus open partial nephrectomy: comparison of outcomes. A systematic review. Minerva urologica e nefrologica = The Italian journal of urology and nephrology 71(2): 113-120	- Exclude - For review C. Proportion of patients stage T3 < 90%
Gross, Evan E, Li, Mingjia, Yin, Ming et al. (2023) A multicenter study assessing survival in patients with metastatic renal cell carcinoma receiving immune checkpoint inhibitor therapy with and without cytoreductive nephrectomy. Urologic oncology 41(1): 51e25-51e31	- Mixed population of SACT pre/post non-pharmacological regimens
Gu, Liangyou, Liu, Kan, Shen, Donglai et al. (2020) Comparison of Robot-Assisted and Laparoscopic Partial Nephrectomy for Completely Endophytic Renal Tumors: A High-Volume Center Experience. Journal of endourology 34(5): 581-587	- Exclude review C - Study included only patients T1-T2
Gu, Liangyou, Ma, Xin, Gao, Yu et al. (2017) Robotic versus Open Level I-II Inferior Vena Cava Thrombectomy: A Matched Group Comparative Analysis. The Journal of urology 198(6): 1241-1246	- Non-OECD country
Gu, Liangyou, Ma, Xin, Wang, Baojun et al. (2018) Laparoscopic vs robot-assisted partial nephrectomy for renal tumours of >4 cm: a propensity score-based analysis. BJU international 122(3): 449-455	- Exclude - For review C. Proportion of patients stage T3 < 90%
Guan, Wei, Bai, Jian, Liu, Jihong et al. (2012) Microwave ablation versus partial nephrectomy for small renal tumors: intermediate-term results. Journal of surgical oncology 106(3): 316-21	- Non-OECD country
Guglielmetti, Giuliano B, Dos Anjos, Gabriel C, Sawczyn, Guilherme et al. (2022) A Prospective,	- Exclude - For review C. Proportion of patients stage T3 < 90%

Study	Reason
Randomized Trial Comparing the Outcomes of Open vs Laparoscopic Partial Nephrectomy. The Journal of urology 208(2): 259-267	
Guillotreau, Julien, Haber, Georges-Pascal, Autorino, Riccardo et al. (2012) Robotic partial nephrectomy versus laparoscopic cryoablation for the small renal mass. European urology 61(5): 899-904	- Primary study covered fully by an included systematic review
Guner, E. and Sahin, S. (2019) Comparison of robotic and laparoscopic partial nephrectomy in robotic surgery era. Bulletin of Urooncology 18(4): 154-157	- There is no information on cT or pT stage
Gupta, K., Omil-Lima, D., Sheyn, D. et al. (2021) Temporal improvements in renal surgery outcomes across surgical approaches. International Urology and Nephrology 53(7): 1311-1316	- Study does not contain a relevant outcome
Haber, Georges-Pascal, White, Wesley M, Crouzet, Sebastien et al. (2010) Robotic versus laparoscopic partial nephrectomy: single-surgeon matched cohort study of 150 patients. Urology 76(3): 754-8	- Not a relevant study design *Consecutive case series*
Hahn, Andrew W, Kotecha, Ritesh R, Viscuse, Paul V et al. (2023) Cytoreductive Nephrectomy for Patients with Metastatic Sarcomatoid and/or Rhabdoid Renal Cell Carcinoma Treated with Immune Checkpoint Therapy. European urology focus 9(5): 734-741	- Mixed population of SACT pre/post non-pharmacological regimens
Hakam, Nizar, Heidar, Nassib Abou, El-Asmar, Jose et al. (2023) Comparative analysis of partial versus radical nephrectomy for renal cell carcinoma: Is oncologic safety compromised during nephron sparing in higher stage disease?. Urology annals 15(2): 226-231	- Non-OECD country
Hall, Mary E, Bhindi, Bimal, Luckenbaugh, Amy N et al. (2021) Association between cytoreductive nephrectomy and survival among patients with metastatic renal cell carcinoma receiving modern therapies: a systematic review and meta-analysis examining effect modification according to systemic therapy approach. Cancer causes & control : CCC 32(7): 675-680	- Mixed population of SACT pre/post non-pharmacological regimens
Haramis, Georgios, Graversen, Joseph A, Mues, Adam C et al. (2012) Retrospective comparison of laparoscopic partial nephrectomy	- Primary study covered fully by an included systematic review

Study	Reason
versus laparoscopic renal cryoablation for small (<3.5 cm) cortical renal masses. Journal of laparoendoscopic & advanced surgical techniques. Part A 22(2): 152-7	
Harke, N.N., Mandel, P., Witt, J.H. et al. (2018) Are there limits of robotic partial nephrectomy? TRIFECTA outcomes of open and robotic partial nephrectomy for completely endophytic renal tumors. Journal of Surgical Oncology 118(1): 206-211	- Not a relevant study design *Consecutive case series*
Harryman, O.A., Davenport, K., Keoghane, S. et al. (2009) A Comparative Study of Quality of Life Issues Relating to Open Versus Laparoscopic Nephrectomy: A Prospective Pragmatic Study. Journal of Urology 181(3): 998-1003	- There is no information on cT or pT stage
Harshman, Lauren C, Yu, R James, Allen, Genevera I et al. (2013) Surgical outcomes and complications associated with presurgical tyrosine kinase inhibition for advanced renal cell carcinoma (RCC). Urologic oncology 31(3): 379-85	- Not a relevant study design *Reports case series*
Hatayama, Tomoya, Tasaka, Ryo, Mochizuki, Hideki et al. (2022) Comparison of surgical outcomes and split renal function between laparoscopic and robot-assisted partial nephrectomy: a propensity score-matched analysis. International urology and nephrology 54(4): 805-811	- There is no information on cT or pT stage
He, Liru, Liu, Yang, Han, Hui et al. (2020) Survival Outcomes After Adding Stereotactic Body Radiotherapy to Metastatic Renal Cell Carcinoma Patients Treated With Tyrosine Kinase Inhibitors. American journal of clinical oncology 43(1): 58-63	- Review H - SABR exclude *SABR and SACT given concomitantly*
Health Technology, Wales (2022) Stereotactic ablative radiotherapy (SABR) for the treatment of renal cell carcinoma.	- Systematic review used as source of primary studies
Heng, Daniel Y C, Wells, J Connor, Rini, Brian I et al. (2014) Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. European urology 66(4): 704-10	- Mixed population of SACT pre/post non-pharmacological regimens *Unclear if participants received SACT before or during or after the CN*

Study	Reason
Hoeh, Benedikt, Wenzel, Mike, Eckart, Olivia et al. (2023) Comparison of peri- and intraoperative outcomes of open vs robotic-assisted partial nephrectomy for renal cell carcinoma: a propensity-matched analysis. World journal of surgical oncology 21(1): 189	- Exclude - For review C. Proportion of patients stage T3 < 90%
Hong, Xuwei, Li, Fei, Tang, Kaiqiang et al. (2016) Prognostic value of cytoreductive nephrectomy combined with targeted therapy for metastatic renal cell carcinoma: a meta-analysis. International urology and nephrology 48(6): 967-75	- Exclude - Result reported in the most updated MA
Hori, Shunta, Sakamoto, Keiichi, Onishi, Kenta et al. (2023) Perioperative outcomes of open and robot-assisted partial nephrectomy in patients with renal tumors of moderate to high complexity. Asian journal of surgery 46(6): 2310-2318	- Exclude - review C. Patients with localised tumour
Hsieh, Po-Yen, Hung, Sheng-Chun, Li, Jian-Ri et al. (2021) The effect of metastasectomy on overall survival in metastatic renal cell carcinoma: A systematic review and meta-analysis. Urologic oncology 39(7): 422-430	- Non-OECD country
Hu, Xu, Wang, Yaohui, Shao, Yanxiang et al. (2023) Radical versus partial nephrectomy for T1 non-clear cell renal cell carcinoma. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 49(8): 1519-1523	- SEER database overlap
Huang, Jiwei, Zhang, Jin, Wang, Yanqing et al. (2016) Comparing Zero Ischemia Laparoscopic Radio Frequency Ablation Assisted Tumor Enucleation and Laparoscopic Partial Nephrectomy for Clinical T1a Renal Tumor: A Randomized Clinical Trial. The Journal of urology 195(6): 1677-83	- Study does not contain a relevant intervention *Radio frequency ablation group also had tumour enucleation*
Huang, Ryan S, Chow, Ronald, Benour, Ali et al. (2025) Comparative efficacy and safety of ablative therapies in the management of primary localised renal cell carcinoma: a systematic review and meta-analysis. The Lancet. Oncology	- Data not reported in an extractable format
Hutchinson, Ryan, Singla, Nirmish, Krabbe, Laura-Maria et al. (2017) Increased use of antihypertensive medications after partial	- Primary study covered fully by an included systematic review

Study	Reason
nephrectomy vs. radical nephrectomy. Urologic oncology 35(11): 660e17-660e25	
Iisager, Laura, Ahrenfeldt, Johanne, Donskov, Frede et al. (2024) Multicenter randomized trial of deferred cytoreductive nephrectomy in synchronous metastatic renal cell carcinoma receiving checkpoint inhibitors: the NORDIC-SUN-Trial. BMC cancer 24(1): 260	- study protocol
Ingels, A, Bensalah, K, Beauval, J B et al. (2022) Comparison of open and robotic-assisted partial nephrectomy approaches using multicentric data (UroCCR-47 study). Scientific reports 12(1): 18981	- Exclude - For review C. Proportion of patients stage T3 < 90%
Ingrosso, Gianluca, Becherini, Carlotta, Francolini, Giulio et al. (2021) Stereotactic body radiotherapy (SBRT) in combination with drugs in metastatic kidney cancer: A systematic review. Critical reviews in oncology/hematology 159: 103242	- Systematic review used as source of primary studies
Izol, Volkan, Gokalp, Fatih, Sozen, Sinan et al. (2021) Factors affecting long-term renal functions after partial vs radical nephrectomy for clinical T1 renal masses: A Multicentre Study of the Urooncology Association, Turkey. International journal of clinical practice 75(5): e13960	- More recent systematic review included that covers the same topic *'requirement of dialysis' could mean eGFR <15 see rec 1.1.3 within NG107. Also from Ochoa:"Due to the heterogeneity of defining CKD across studies, we pooled the studies for stages III-V or IV-V as determined by the EGFR or by renal replacement therapy and kidney transplant" Not included in Ochoa most likely because data not reported as HR/OR - to exclude*
Jang, Hoon Ah, Kim, Jin Wook, Byun, Seok Soo et al. (2016) Oncologic and Functional Outcomes after Partial Nephrectomy Versus Radical Nephrectomy in T1b Renal Cell Carcinoma: A Multicenter, Matched Case-Control Study in Korean Patients. Cancer research and treatment 48(2): 612-20	- Primary study covered fully by an included systematic review
Jang, Hyeon Jun, Song, Wan, Suh, Yoon Seok et al. (2014) Comparison of perioperative outcomes of robotic versus laparoscopic partial nephrectomy for complex renal tumors (RENAL nephrometry score of 7 or higher). Korean journal of urology 55(12): 808-13	- There is no information on cT or pT stage
Janisch, Florian, Hillemacher, Tobias, Fuehner, Constantin et al. (2020) The impact of cytoreductive nephrectomy on survival	- Data not reported in an extractable format *Reports OS, PFS and CSS as median months*

Study	Reason
outcomes in patients treated with tyrosine kinase inhibitors for metastatic renal cell carcinoma in a real-world cohort. Urologic oncology 38(9): 739e9-739e15	
Jelley, C.R., Kurukulaarachchi, K.A.S.H., Forster, L. et al. (2017) Comparison of open and robotic nephron sparing surgery: a single centre experience. Journal of Clinical Urology 10(1): 28-35	- Exclude review C. Study included only patients T1-T2
Jeon, Hwang Gyun, Jeong, In Gab, Lee, Jeong Woo et al. (2009) Prognostic factors for chronic kidney disease after curative surgery in patients with small renal tumors. Urology 74(5): 1064-8	- Primary study covered fully by an included systematic review
Jeong, In Gab, Khandwala, Yash S, Kim, Jae Heon et al. (2017) Association of Robotic-Assisted vs Laparoscopic Radical Nephrectomy With Perioperative Outcomes and Health Care Costs, 2003 to 2015. JAMA 318(16): 1561-1568	- There is no information on cT or pT stage
Jeong, Seung-Hwan, Kim, Jung Kwon, Park, Juhyun et al. (2016) Pathological T3a Upstaging of Clinical T1 Renal Cell Carcinoma: Outcomes According to Surgical Technique and Predictors of Upstaging. PloS one 11(11): e0166183	- Comparator in study does not match that specified in protocol
Ji, B., Li, D., Fu, S. et al. (2020) Propensity-score matched comparison of partial versus radical nephrectomy for T1N0M0 sarcomatoid renal cell carcinoma. Translational Andrology and Urology 9(2): 250-257	- SEER database overlap
Ji, Changwei, Zhao, Xiaozhi, Zhang, Shiwei et al. (2016) Laparoscopic Radiofrequency Ablation versus Partial Nephrectomy for cT1a Renal Tumors: Long-Term Outcome of 179 Patients. Urologia internationalis 96(3): 345-53	- Non-OECD country
Jiang, Jianping, Zheng, Xiangyi, Qin, Jie et al. (2009) Health-related quality of life after hand-assisted laparoscopic and open radical nephrectomies of renal cell carcinoma. International urology and nephrology 41(1): 23-7	- Exclude - For review C. Proportion of patients stage T3 < 90%
Jiang, Yu-Li, Peng, Cheng-Xia, Wang, Heng-Zi et al. (2019) Comparison of the long-term follow-up and perioperative outcomes of partial nephrectomy and radical nephrectomy for 4 cm to 7 cm renal cell carcinoma: a systematic review and meta-analysis. BMC urology 19(1): 48	- Systematic review used as source of primary studies

Study	Reason
Jiang, Yu-Li, Yu, Dong-Dong, Xu, Yang et al. (2023) Comparison of perioperative outcomes of robotic vs. laparoscopic partial nephrectomy for renal tumors with a RENAL nephrometry score >=7: A meta-analysis. Frontiers in surgery 10: 1138974	- Exclude - For review C. Proportion of patients stage T3 < 90%
Jin, Seok-Joon, Park, Jun-Young, Kim, Doo-Hwan et al. (2017) Comparison of postoperative pain between laparoscopic and robot-assisted partial nephrectomies for renal tumors: A propensity score matching analysis. Medicine 96(29): e7581	- Exclude - For review C. Proportion of patients stage T3 < 90%
Jokimaki, A., Hietala, H., Lemma, J. et al. (2023) Previous radiotherapy improves treatment responses and causes a trend toward longer time to progression among patients with immune checkpoint inhibitor-related adverse events. Cancer Immunology, Immunotherapy 72(10): 3337-3347	- Review H - SABR exclude *Protocol relevant outcomes are not reported for RCC subgroup*
Jones, J.O., Ince, W.H.J., Welsh, S.J. et al. (2022) Activity of Immunotherapy Regimens on Primary Renal Tumours: A Systematic Review. Kidney Cancer 6(4): 221-236	- Systematic review used as source of primary studies
Joslyn, Sue A; Sirintrapun, S Joseph; Konety, Badrinath R (2005) Impact of lymphadenectomy and nodal burden in renal cell carcinoma: retrospective analysis of the National Surveillance, Epidemiology, and End Results database. Urology 65(4): 675-80	- There is no information on cT or pT stage
Junker, Theresa, Duus, Louise, Rasmussen, Benjamin S B et al. (2022) Quality of life and complications after nephron-sparing treatment of renal cell carcinoma stage T1-a systematic review. Systematic reviews 11(1): 4	- Systematic review used as source of primary studies
Kalogirou, Charis, Fender, Hendrik, Muck, Patricia et al. (2017) Long-Term Outcome of Nephron-Sparing Surgery Compared to Radical Nephrectomy for Renal Cell Carcinoma >=4 cm - A Matched-Pair Single Institution Analysis. Urologia internationalis 98(2): 138-147	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Kandi, Maryam, Richard, Patrick O, Violette, Philippe D et al. (2024) Complications and blood loss after invasive treatments for small renal masses: A systematic review. Canadian Urological Association journal = Journal de l'Association des urologues du Canada	- Comparator in study does not match that specified in protocol

Study	Reason
Kaneko, Gou, Miyajima, Akira, Kikuchi, Eiji et al. (2012) The benefit of laparoscopic partial nephrectomy in high body mass index patients. Japanese journal of clinical oncology 42(7): 619-24	- Exclude - review C - Study included only patients T1-T2
Kapoor, A., Wong, E.C.L., Fang, W. et al. (2019) Upfront cytoreductive nephrectomy vs. Upfront systemic therapy in metastatic kidney cancer. Canadian Urological Association Journal 13(11): e377-e381	- Data not reported in an extractable format *Protocol relevant outcomes reported as median, no time to event data*
Kato, Daiki, Nakane, Keita, Enomoto, Torai et al. (2021) The utility of laparoscopic partial nephrectomy with renal function preservation, regardless of warm ischemia time, compared with laparoscopic radical nephrectomy. Asian journal of endoscopic surgery 14(3): 386-393	- Data not reported in an extractable format
Kato, Renpei, Naito, Sei, Numakura, Kazuyuki et al. (2022) Significance of upfront cytoreductive nephrectomy stratified by IMDC risk for metastatic renal cell carcinoma in targeted therapy era - a multi-institutional retrospective study. International journal of clinical oncology 27(3): 563-573	- Mixed population of SACT pre/post non-pharmacological regimens
Katsanos, K, Mailli, L, Krokidis, M et al. (2014) Systematic review and meta-analysis of thermal ablation versus surgical nephrectomy for small renal tumours. Cardiovascular and interventional radiology 37(2): 427-37	- More recent systematic review included that covers the same topic
Katsimperis, Stamatios, Tzelves, Lazaros, Bellos, Themistoklis et al. (2022) Cytoreductive nephrectomy for synchronous metastatic renal cell carcinoma. Is there enough evidence?. Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica 94(4): 476-485	- Systematic review used as source of primary studies
Kawase, Kota, Enomoto, Torai, Kawase, Makoto et al. (2022) The Impact of Postoperative Renal Function Recovery after Laparoscopic and Robot-Assisted Partial Nephrectomy in Patients with Renal Cell Carcinoma. Medicina (Kaunas, Lithuania) 58(4)	- Exclude - For review C . Proportion of patients stage T3 < 90%
Khalifeh, Ali, Autorino, Riccardo, Hillyer, Shahab P et al. (2013) Comparative outcomes and assessment of trifecta in 500 robotic and laparoscopic partial nephrectomy cases: a	- Exclude - For review C. Proportion of patients stage T3 < 90%

Study	Reason
single surgeon experience. The Journal of urology 189(4): 1236-42	
Khalil, M.I., Ubeda, J., Soehner, T. et al. (2019) Contemporary Perioperative Morbidity and Mortality Rates of Minimally Invasive vs Open Partial Nephrectomy in Obese Patients with Kidney Cancer. Journal of Endourology 33(11): 920-927	- There is no information on cT or pT stage
Khan, M.M.A., Patel, R.A., Jain, N. et al. (2019) Prospective analysis of laparoscopic versus open radical nephrectomy for renal tumours more than 7 cm. Journal of Minimal Access Surgery 15(1): 14-18	- Non-OECD country - There is no information on cT or pT stage
Kim, Jeong Ho, Park, Yong Hyun, Kim, Yong June et al. (2015) Perioperative and long-term renal functional outcomes of robotic versus laparoscopic partial nephrectomy: a multicenter matched-pair comparison. World journal of urology 33(10): 1579-84	- There is no information on cT or pT stage
Kim, Jung Kwon, Lee, Hakmin, Oh, Jong Jin et al. (2019) Comparison of robotic and open partial nephrectomy for highly complex renal tumors (RENAL nephrometry score >=10). PloS one 14(1): e0210413	- Exclude - For review C. Proportion of patients stage T3 < 90%
Kim, Na Young, Lee, Hye Sun, Park, Jin Ha et al. (2022) Influence of age on gender-related differences in acute kidney injury after minimally invasive radical or partial nephrectomy. Surgical endoscopy 36(5): 2962-2972	- Study does not contain a relevant outcome
Kim, Simon P, Thompson, R Houston, Boorjian, Stephen A et al. (2012) Comparative effectiveness for survival and renal function of partial and radical nephrectomy for localized renal tumors: a systematic review and meta-analysis. The Journal of urology 188(1): 51-7	- Systematic review used as source of primary studies
Kim, Sung Han, Jeong, Kyung-Chae, Joung, Jae Young et al. (2018) Prognostic significance of nephrectomy in metastatic renal cell carcinoma treated with systemic cytokine or targeted therapy: A 16-year retrospective analysis. Scientific reports 8(1): 2974	- Study does not contain a relevant intervention *Mixed population, receiving radical nephrectomy and CN*
Kim, Sung Han, Lee, Eun-Sik, Kim, Hyeon Hoe et al. (2015) A propensity-matched comparison of perioperative complications and of chronic kidney disease between robot-assisted	- Primary study covered fully by an included systematic review

Study	Reason
laparoscopic partial nephrectomy and radiofrequency ablative therapy. Asian journal of surgery 38(3): 126-33	
Kim, Sung Han, Park, Boram, Hwang, Eu Chang et al. (2021) A Retrospective, Multicenter, Long-Term Follow-Up Analysis of the Prognostic Characteristics of Recurring Non-Metastatic Renal Cell Carcinoma After Partial or Radical Nephrectomy. Frontiers in oncology 11: 653002	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Kizilay, Fuat, Turna, Burak, Apaydin, Erdal et al. (2019) Comparison of long-term outcomes of laparoscopic and robot-assisted laparoscopic partial nephrectomy. The Kaohsiung journal of medical sciences 35(4): 238-243	- Comparator in study does not match that specified in protocol
Klatte, Tobias, Berni, Alessandro, Serni, Sergio et al. (2021) Intermediate- and long-term oncological outcomes of active surveillance for localized renal masses: a systematic review and quantitative analysis. BJU international 128(2): 131-143	- More recent systematic review included that covers the same topic *Single arm studies*
Klatte, Tobias, Fife, Kate, Welsh, Sarah J et al. (2018) Prognostic effect of cytoreductive nephrectomy in synchronous metastatic renal cell carcinoma: a comparative study using inverse probability of treatment weighting. World journal of urology 36(3): 417-425	- Mixed population of SACT pre/post non-pharmacological regimens
Klatte, Tobias, Grubmuller, Bernhard, Waldert, Matthias et al. (2011) Laparoscopic cryoablation versus partial nephrectomy for the treatment of small renal masses: systematic review and cumulative analysis of observational studies. European urology 60(3): 435-43	- Review article but not a systematic review
Klatte, Tobias; Shariat, Shahrokh F; Remzi, Mesut (2014) Systematic review and meta-analysis of perioperative and oncologic outcomes of laparoscopic cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal tumors. The Journal of urology 191(5): 1209-17	- More recent systematic review included that covers the same topic
Kobayashi, Satoshi, Mutaguchi, Jun, Kashiwagi, Eiji et al. (2021) Clinical advantages of robot-assisted partial nephrectomy versus laparoscopic partial nephrectomy in terms of global and split renal functions: A propensity score-matched comparative analysis.	- Exclude - For review C. Proportion of patients stage T3 < 90%

Study	Reason
International journal of urology : official journal of the Japanese Urological Association 28(6): 630-636	
Kokorovic, Andrea and Rendon, Ricardo A (2019) Cytoreductive nephrectomy in metastatic kidney cancer: what do we do now?. Current opinion in supportive and palliative care 13(3): 255-261	- Review article but not a systematic review
Komninos, Christos, Shin, Tae Young, Tuliao, Patrick et al. (2014) R-LESS partial nephrectomy trifecta outcome is inferior to multiport robotic partial nephrectomy: comparative analysis. European urology 66(3): 512-7	- There is no information on cT or pT stage
Koo, Kyo Chul, Kim, Jong Chan, Cho, Kang Su et al. (2016) Oncological outcomes after partial vs radical nephrectomy in renal cell carcinomas of <=7 cm with presumed renal sinus fat invasion on preoperative imaging. BJU international 117(1): 87-93	- Not a relevant study design *Consecutive case series*
Kopp, Ryan P, Mehrazin, Reza, Palazzi, Kerrin L et al. (2014) Survival outcomes after radical and partial nephrectomy for clinical T2 renal tumours categorised by R.E.N.A.L. nephrometry score. BJU international 114(5): 708-18	- Secondary publication of an included study that does not provide any additional relevant information
Kowalewski, Karl-Friedrich, Muller, Dennis, Kirchner, Marietta et al. (2021) Robotic-Assisted Versus Conventional Open Partial Nephrectomy (Robocop): A Propensity Score-Matched Analysis of 249 Patients. Urologia internationalis 105(56): 490-498	- There is no information on cT or pT stage
Krabbe, Laura-Maria, Haddad, Ahmed Q, Westerman, Mary E et al. (2014) Surgical management of metastatic renal cell carcinoma in the era of targeted therapies. World journal of urology 32(3): 615-22	- Review article but not a systematic review
Kroeze, Stephanie G C, Fritz, Corinna, Schaule, Jana et al. (2021) Stereotactic radiotherapy combined with immunotherapy or targeted therapy for metastatic renal cell carcinoma. BJU international 127(6): 703-711	- Mixed population of SACT pre/post non-pharmacological regimens *76% of the participants received SACT before SRT, no subgroup results reported*
Kunath, Frank, Schmidt, Stefanie, Krabbe, Laura-Maria et al. (2017) Partial nephrectomy versus radical nephrectomy for clinical localised	- Systematic review used as source of primary studies

Study	Reason
renal masses. The Cochrane database of systematic reviews 5: cd012045	
Kunkle, David A; Egleston, Brian L; Uzzo, Robert G (2008) Excise, ablate or observe: the small renal mass dilemma--a meta-analysis and review. The Journal of urology 179(4): 1227-4	- More recent systematic review included that covers the same topic
Kwak, Cheol, Park, Yong Hyun, Jeong, Chang Wook et al. (2007) No role of adjuvant systemic therapy after complete metastasectomy in metastatic renal cell carcinoma?. Urologic oncology 25(4): 310-6	- Comparator in study does not match that specified in protocol *All included participants had undergone complete metastasectomy. Compares SACT vs. No SACT population.*
Kwak, Cheol, Park, Yong Hyun, Jeong, Chang Wook et al. (2007) Metastasectomy without systemic therapy in metastatic renal cell carcinoma: comparison with conservative treatment. Urologia internationalis 79(2): 145-51	- Study does not contain a relevant intervention *None of the participants received SACT at anytime point. Study compares metastasectomy vs. no metastasectomy after nephrectomy*
La Vecchia, Maria, Federico, Manuela, Aiello, Dario et al. (2024) The Role of Stereotactic Body Radiotherapy (SBRT) in Oligoprogressive Renal Cell Carcinoma (RCC) Treated with ICIs-TKIs: A Retrospective Multicentric Study. Journal of personalized medicine 14(10)	- Comparator in study does not match that specified in protocol *There isn't a defined comparator group. Outcomes were reported for some patients before SBRT but these outcomes did not meet the protocol criteria and these patients did go on to have SBRT also.*
Laganosky, D., Filson, C.P., Patil, D. et al. (2020) Survival benefit with extended lymphadenectomy for advanced renal malignancy: A population-based analysis. Asian Journal of Urology 7(1): 29-36	- Comparator in study does not match that specified in protocol
Lai, G.-S., Li, J.-R., Wang, S.-S. et al. (2020) Survival analysis of pathological T3a upstaging in clinical T1 renal cell carcinoma. In Vivo 34(2): 799-805	- Non-OECD country
Lai, Gu-Shun, Li, Jian-Ri, Wang, Shian-Shiang et al. (2024) Outcome benefits of upfront cytoreductive nephrectomy for patients with metastatic renal cell carcinoma: An analysis of the TriNetX database. PloS one 19(3): e0299102	- Non-OECD country
Lai, T.C.T.; Ma, W.K.; Yiu, M.K. (2016) Partial nephrectomy for t1 renal cancer can achieve an equivalent oncological outcome to radical nephrectomy with better renal preservation: The way to go. Hong Kong Medical Journal 22(1): 39-45	- Primary study covered fully by an included systematic review

Study	Reason
Lam, Jing Kai Jackie; Tan, Sher Yin; Chong, Kian Tai (2020) Is partial nephrectomy worth performing compared to radical nephrectomy for small, localised renal cortical tumours in geriatric patients?. Singapore medical journal 61(4): 190-193	- Data not reported in an extractable format *reports CKD at 5 years but it was published within the search dates of Ochoa-Arvizo - But N at 5yrs was not reported, which is likely why it wasn't included in Ochoa*
Larcher, A, Sun, M, Dell'Oglio, P et al. (2017) Mortality, morbidity and healthcare expenditures after local tumour ablation or partial nephrectomy for T1A kidney cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 43(4): 815-822	- Data not reported in an extractable format *Insufficient data reported to assess study methodology*
Larcher, Alessandro, Meskawi, Malek, Valdivieso, Roger et al. (2016) Comparison of renal function detriments after local tumor ablation or partial nephrectomy for renal cell carcinoma. World journal of urology 34(3): 383-9	- Data not reported in an extractable format *Insufficient information reported to assess study*
Laru, Lauri, Ronkainen, Hanna, Ohtonen, Pasi et al. (2021) Nephrectomy improves the survival of metastatic renal cell cancer patients with moderate to good performance status-results from a Finnish nation-wide population-based study from 2005 to 2010. World journal of surgical oncology 19(1): 190	- Comparator in study does not match that specified in protocol *Study compares CN vs. metastasectomy. Does not report about the SACT status*
Lasorsa, Francesco, Bignante, Gabriele, Orsini, Angelo et al. (2024) Partial nephrectomy in elderly patients: a systematic review and analysis of comparative outcomes. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 50(10): 108578	- Systematic review used as source of primary studies
Le Guevelou, Jennifer, Sargos, Paul, Siva, Shankar et al. (2023) The Emerging Role of Extracranial Stereotactic Ablative Radiotherapy for Metastatic Renal Cell Carcinoma: A Systematic Review. European urology focus 9(1): 114-124	- Systematic review used as source of primary studies
Lee, H., Lee, M., Lee, S.E. et al. (2018) Outcomes of pathologic stage T3a renal cell carcinoma up-staged from small renal tumor: Emphasis on partial nephrectomy. BMC Cancer 18(1): 427	- Study does not contain a relevant intervention

Study	Reason
Lee, Nora G; Zampini, Anna; Tuerk, Ingolf (2012) Single surgeon's experience with laparoscopic versus robotic partial nephrectomy: perioperative outcomes/complications and influence of tumor characteristics on choice of therapy. The Canadian journal of urology 19(5): 6465-70	- Exclude - review C - study included only patients T1-T2
Lee, Sangchul, Oh, Jongjin, Hong, Seong Kyu et al. (2011) Open versus robot-assisted partial nephrectomy: effect on clinical outcome. Journal of endourology 25(7): 1181-5	- There is no information on cT or pT stage
Lee, Sangchul; Ryu, Hoyoung; Lee, Jeong Woo (2021) Open Partial Nephrectomy vs. Robot-assisted Partial Nephrectomy for a Renal Tumor Larger than 4 cm: a Propensity Score Matching Analysis. Journal of Korean medical science 36(20): e135	- Exclude - For review C. Proportion of patients stage T3 < 90%
Lenis, A.T., Salmasi, A.H., Donin, N.M. et al. (2018) Trends in usage of cytoreductive partial nephrectomy and effect on overall survival in patients with metastatic renal cell carcinoma. Urologic Oncology: Seminars and Original Investigations 36(2): 78e21-78e28	- Comparator in study does not match that specified in protocol *Compares partial CN Vs. radical CN*
Lesnyak, O., Stroy, O., Banyra, O. et al. (2020) Assessment of the effectiveness of radiofrequency ablation as a technique for destroying small renal tumors in patients older than 70. Central European Journal of Urology 73(4): 1-7	- Non-OECD country
Li, G, Luo, Q, Lang, Z et al. (2018) Histopathologic analysis of stage pT1b kidney neoplasms for optimal surgical margins of nephron-sparing surgery. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico 20(9): 1196-1201	- Study does not contain a relevant outcome
Li, Jingdong, Zhang, Yanping, Teng, Zhihai et al. (2019) Partial nephrectomy versus radical nephrectomy for cT2 or greater renal tumors: a systematic review and meta-analysis. Minerva urologica e nefrologica = The Italian journal of urology and nephrology 71(5): 435-444	- Systematic review used as source of primary studies
Li, Jinze, Peng, Lei, Cao, Dehong et al. (2020) Comparison of Perioperative Outcomes of Robot-Assisted vs. Laparoscopic Radical	- Exclude - For review C. Proportion of patients stage T3 < 90%

Study	Reason
Nephrectomy: A Systematic Review and Meta-Analysis. Frontiers in oncology 10: 551052	
Li, Kun-Peng, Chen, Si-Yu, Wan, Shun et al. (2024) Percutaneous ablation versus robotic-assisted partial nephrectomy for cT1 renal cell carcinoma: an evidence-based analysis of comparative outcomes. Journal of robotic surgery 18(1): 301	- Systematic review used as source of primary studies
Li, Kun-Peng, Chen, Si-Yu, Wang, Chen-Yang et al. (2023) The impact of cytoreductive nephrectomy on survival outcomes in patients with metastatic renal cell carcinoma receiving immunotherapy: An evidence-based analysis of comparative outcomes. Frontiers in immunology 14: 1132466	- Exclude - wrong population
Li, Kun-Peng, Chen, Si-Yu, Wang, Chen-Yang et al. (2023) Comparison between minimally invasive partial nephrectomy and open partial nephrectomy for complex renal tumors: a systematic review and meta-analysis. International journal of surgery (London, England) 109(6): 1769-1782	- Exclude - For review C. Proportion of patients stage T3 < 90%
Li, Kun-Peng, Wan, Shun, Chen, Si-Yu et al. (2024) Perioperative, functional and oncologic outcomes of percutaneous ablation versus minimally invasive partial nephrectomy for clinical T1 renal tumors: outcomes from a pooled analysis. Journal of robotic surgery 18(1): 306	- Systematic review used as source of primary studies
Li, Kun-Peng, Wan, Shun, Wang, Chen-Yang et al. (2023) Perioperative, functional, and oncologic outcomes of robot-assisted versus open partial nephrectomy for complex renal tumors (RENAL score >= 7): an evidence-based analysis. Journal of robotic surgery 17(4): 1247-1258	- Exclude - For review C. Proportion of patients stage T3 < 90%
Li, Pin, Peng, Cheng, Gu, Liangyou et al. (2019) Radical Nephrectomy with or without Lymph Node Dissection for pT3 Renal Cell Carcinoma: A Propensity Score-based Analysis. Journal of Cancer 10(10): 2369-2375	- Non-OECD country - Comparator in study does not match that specified in protocol
Li, Wentao, Cheng, Yanlei, Cheng, Yi et al. (2014) Clinical efficacy of radical nephrectomy versus nephron-sparing surgery on localized renal cell carcinoma. European journal of medical research 19: 58	- Systematic review used as source of primary studies

Study	Reason
Liao, Xinyang, Qiu, Shi, Wang, Wanyu et al. (2019) Partial nephrectomy vs cryoablation for T1a renal cell carcinoma: A comparison of survival benefit stratified by tumour size. Cancer epidemiology 59: 221-226	- Non-OECD country
Liek, Elisabeth, Elsebach, Klaus, Gobel, Hubert et al. (2018) The Overall Survival Benefit for Patients with T1 Renal Cell Carcinoma after Nephron-Sparing Surgery Depends on Gender and Age. Urologia internationalis 100(3): 309-316	- Data not reported in an extractable format *Overall survival reported as Kaplan-Meier and P values*
Lin, J., Song, A.J., Hoffman-Censits, J. et al. (2020) A Pilot Study of Radiation Therapy in Combination with Pembrolizumab in Patients with Metastatic Renal Cell Cancer. American Journal of Clinical Oncology: Cancer Clinical Trials 43(2): 82-86	- Not a relevant study design *Reports a part of RCT. Reported subgroup irrelevant to the protocol*
Lin, Pengxiu, Wu, Minhong, Gu, Hongyong et al. (2021) Comparison of outcomes between laparoscopic and robot-assisted partial nephrectomy for complex renal tumors: RENAL score >=7 or maximum tumor size >4 cm. Minerva urology and nephrology 73(2): 154-164	- Exclude review C - Study included only patients T1-T2
Lin, Wenhao, Yang, Zhenggang, Yan, Ling et al. (2023) Comparison of partial nephrectomy and radical nephrectomy for cystic renal cell carcinoma: a SEER-based and retrospective study. Scientific reports 13(1): 8052	- SEER database overlap
Liu, Changfu, Cao, Fei, Xing, Wenge et al. (2019) Efficacy of cryoablation combined with sorafenib for the treatment of advanced renal cell carcinoma. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group 36(1): 220-228	- Study does not contain a relevant intervention *SACT given along with cryotherapy*
Liu, Gang, Ma, Yulei, Wang, Shouhua et al. (2017) Laparoscopic Versus Open Radical Nephrectomy for Renal Cell Carcinoma: a Systematic Review and Meta-Analysis. Translational oncology 10(4): 501-510	- Exclude - For review C. Proportion of patients stage T3 < 90%
Liu, H.; Gao, C.; Yu, H. (2016) Safety and effectiveness of percutaneous radiofrequency ablation in early stage renal cell carcinoma. Oncology Letters 12(6): 4618-4622	- Non-OECD country

Study	Reason
Liu, Hui, Kong, Qing-Fang, Li, Jian et al. (2021) A meta-analysis for comparison of partial nephrectomy vs. radical nephrectomy in patients with pT3a renal cell carcinoma. Translational andrology and urology 10(3): 1170-1178	- Comparator in study does not match that specified in protocol *PN vs RN for T3 tumour*
Liu, Ning, Huang, Daoguang, Cheng, Xiangming et al. (2017) Percutaneous radiofrequency ablation for renal cell carcinoma vs. partial nephrectomy: Comparison of long-term oncologic outcomes in both clear cell and non-clear cell of the most common subtype. Urologic oncology 35(8): 530e1-530e6	- Non-OECD country
Liu, Wing K, Lam, J M, Butters, T et al. (2020) Cytoreductive nephrectomy in metastatic renal cell carcinoma: outcome of patients treated with a multidisciplinary, algorithm-driven approach. World journal of urology 38(12): 3199-3205	- Mixed population of SACT pre/post non-pharmacological regimens
Liu, X-H, Song, J, Ma, W-M et al. (2024) Comparison of perioperative outcomes between robot-assisted partial nephrectomy and laparoscopic partial nephrectomy in obese patients. European review for medical and pharmacological sciences 28(10): 3583-3589	- Exclude - Review C. Patients with localised tumour
Liu, Y., Zhang, Z., Han, H. et al. (2021) Survival After Combining Stereotactic Body Radiation Therapy and Tyrosine Kinase Inhibitors in Patients With Metastatic Renal Cell Carcinoma. Frontiers in Oncology 11: 607595	- Study does not contain a relevant outcome
Liu, Yang, Long, Wen, Zhang, Zhiling et al. (2021) Metastasis-directed stereotactic body radiotherapy for oligometastatic renal cell carcinoma: extent of tumor burden eradicated by radiotherapy. World journal of urology 39(11): 4183-4190	- Mixed population of SACT pre/post non-pharmacological regimens - Review H - SABR exclude
Liu, Yang, Zhang, Zhiling, Liu, Ruiqi et al. (2021) Stereotactic body radiotherapy in combination with non-frontline PD-1 inhibitors and targeted agents in metastatic renal cell carcinoma. Radiation oncology (London, England) 16(1): 211	- Review H - SABR exclude *doesn't separate out SABR given before vs after SACT*
Liu, Ying, Wang, Li, Bao, Er-Hao et al. (2024) Perioperative, functional, and oncological outcomes after cryoablation or partial nephrectomy for small renal masses in solitary kidneys: a systematic review and meta-analysis. BMC urology 24(1): 19	- Systematic review used as source of primary studies

Study	Reason
Liu, Z., Wang, P., Xia, D. et al. (2013) Comparison between laparoscopic and open partial nephrectomy: Surgical, oncologic, and functional outcomes. Kaohsiung Journal of Medical Sciences 29(11): 624-628	- Non-OECD country - Exclude Review C - Study included only patients T1-T2
Liu, Zhenhua, Yang, Zhenyu, Li, Jibin et al. (2023) Partial versus radical nephrectomy for the treatment of pT3aN0M0 renal cell carcinoma: A propensity score analysis. Asian journal of surgery 46(9): 3607-3613	- Comparator in study does not match that specified in protocol *For review C - comparison RN vs PN in T3 tumours which is not applicable for this question*
Ljungberg, Borje, Sundqvist, Pernilla, Lindblad, Per et al. (2020) Survival advantage of upfront cytoreductive nephrectomy in patients with primary metastatic renal cell carcinoma compared with systemic and palliative treatments in a real-world setting. Scandinavian journal of urology 54(6): 487-492	- Comparator in study does not match that specified in protocol *Compares SACT alone with upfront CN.*
Long, Jean-Alexandre, Yakoubi, Rachid, Lee, Byron et al. (2012) Robotic versus laparoscopic partial nephrectomy for complex tumors: comparison of perioperative outcomes. European urology 61(6): 1257-62	- Exclude - review C. Patients with localised tumour
Loo Gan, Chun, Huang, Jiaming, Pan, Elizabeth et al. (2023) Real-world Practice Patterns and Safety of Concurrent Radiotherapy and Cabozantinib in Metastatic Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. European urology oncology 6(2): 204-211	- Review H - SABR exclude - Mixed population of SACT pre/post non-pharmacological regimens
Lounova, Veronika, Student, Vladimir Jr, Purova, Dana et al. (2024) Frequency of benign tumors after partial nephrectomy and the association between malignant tumor findings and preoperative clinical parameters. BMC urology 24(1): 175	- Study did not compare the interventions of interest *Reporting results for benign and malignant tumours and not for the two different surgical techniques for nephrectomy*
Love, Harrison, Yong, Courtney, Slaven, James E et al. (2024) Outcomes of open versus robotic partial nephrectomy: a 20-year single institution experience. Journal of robotic surgery 18(1): 315	- Exclude - For review C. Proportion of patients stage T3 < 90%
Lucas, Steven M, Mellon, Matthew J, Erntsberger, Luke et al. (2012) A comparison of robotic, laparoscopic and open partial nephrectomy. JSLS : Journal of the Society of Laparoendoscopic Surgeons 16(4): 581-7	- Comparator in study does not match that specified in protocol

Study	Reason
Luciani, Lorenzo G, Chiodini, Stefano, Mattevi, Daniele et al. (2017) Robotic-assisted partial nephrectomy provides better operative outcomes as compared to the laparoscopic and open approaches: results from a prospective cohort study. Journal of robotic surgery 11(3): 333-339	- Exclude - For review C. Proportion of patients stage T3 < 90%
Luo, X., Yi, M., Hu, Q. et al. (2019) Is cytoreductive nephrectomy necessary for metastatic renal cell carcinoma: A systematic review and meta-analysis. International Journal of Clinical and Experimental Medicine 12(6): 7029-7037	- Exclude - Result reported in the most updated MA
Luo, X, Li, J-X, Liu, Y-T et al. (2019) Influence of lymph node dissection in patients undergoing radical nephrectomy for non-metastatic renal cell carcinoma: a systematic review and meta-analysis. European review for medical and pharmacological sciences 23(14): 6079-6090	- Exclude - For review C. Proportion of patients stage T3 < 90%
Luo, You, Chen, San-San, Bai, Liang et al. (2017) Nephron Sparing Surgery Has Better Oncologic Outcomes Than Extirpative Nephrectomy in T1a but Not in T1b or T2 Stage Renal Cell Carcinoma. Medical science monitor : international medical journal of experimental and clinical research 23: 3480-3488	- SEER database overlap
Lv, ZongYing, Chen, GuiYuan, Chen, XiaoBin et al. (2023) Open versus robot-assisted partial nephrectomy for highly complex renal masses: a meta-analysis of perioperitive and functional outcomes. Journal of robotic surgery 17(5): 1955-1965	- Exclude - For review C. Proportion of patients stage T3 < 90%
Ma, Ming-Wei, Li, Hong-Zhen, Gao, Xian-Shu et al. (2022) Outcomes of High-Dose Stereotactic Ablative Radiotherapy to All/Multiple Sites for Oligometastatic Renal Cell Cancer Patients. Current oncology (Toronto, Ont.) 29(10): 7832-7841	- Mixed population of SACT pre/post non-pharmacological regimens - Review H - SABR exclude
MacLennan, Steven, Imamura, Mari, Lapitan, Marie C et al. (2012) Systematic review of oncological outcomes following surgical management of localised renal cancer. European urology 61(5): 972-93	- Systematic review used as source of primary studies
MacLennan, Steven, Imamura, Mari, Lapitan, Marie C et al. (2012) Systematic review of perioperative and quality-of-life outcomes	- Systematic review used as source of primary studies

Study	Reason
following surgical management of localised renal cancer. European urology 62(6): 1097-117	
Maisel, Franziska, Smolle, Maria A, Mollnar, Stefanie et al. (2022) Benefit of Metastasectomy in Renal Cell Carcinoma: A Propensity Score Analysis. Clinical genitourinary cancer 20(4): 344-353	- Comparator in study does not match that specified in protocol - Study does not contain a relevant intervention
Malaeb, B.S., Sherwood, J.B., Taylor, G.D. et al. (2005) Hand-assisted laparoscopic nephrectomy for renal masses >9.5 cm: Series comparison with open radical nephrectomy. Urologic Oncology: Seminars and Original Investigations 23(5): 323-327	- Exclude - Review C. Proportion of patients stage T3 < 90%
Manikandan, R; Srinivasan, V; Rane, A (2004) Which is the real gold standard for small-volume renal tumors? Radical nephrectomy versus nephron-sparing surgery. Journal of endourology 18(1): 39-44	- More recent systematic review included that covers the same topic
Marchioni, M., Bandini, M., Pompe, R.S. et al. (2018) The impact of lymph node dissection and positive lymph nodes on cancer-specific mortality in contemporary pT2-3 non-metastatic renal cell carcinoma treated with radical nephrectomy. BJU International 121(3): 383-392	- Comparator in study does not match that specified in protocol *LND vs no LND*
Marchioni, Michele, Cheaib, Joseph G, Takagi, Toshio et al. (2021) Active surveillance for small renal masses in elderly patients does not increase overall mortality rates compared to primary intervention: a propensity score weighted analysis. Minerva urology and nephrology 73(6): 781-788	- Comparator in study does not match that specified in protocol *Ablation and partial nephrectomy groups combined in results vs active surveillance*
Marchioni, Michele, Preisser, Felix, Bandini, Marco et al. (2019) Comparison of Partial Versus Radical Nephrectomy Effect on Other-cause Mortality, Cancer-specific Mortality, and 30-day Mortality in Patients Older Than 75 Years. European urology focus 5(3): 467-473	- Study does not contain a relevant outcome
Margulis, Vitaly, Tamboli, Pheroze, Jacobsohn, Kenneth M et al. (2007) Oncological efficacy and safety of nephron-sparing surgery for selected patients with locally advanced renal cell carcinoma. BJU international 100(6): 1235-9	- Comparator in study does not match that specified in protocol *Compares Rn vs PN in locally advanced RCC - not applicable for review C.*
Maric, P., Jovanovic, M., Milovic, N. et al. (2017) Complications of radical and partial	- Data not reported in an extractable format

Study	Reason
nephrectomy for renal cell carcinoma up to 7 cm. Vojnosanitetski Pregled 74(7): 639-643	*Severe complications (Clavien-Dindo ≥III) were only reported in a graphDuration of hospital stay was reported as median and range*
Mason, Ross J, Atwell, Thomas D, Lohse, Christine et al. (2017) Renal functional outcomes in patients undergoing percutaneous cryoablation or partial nephrectomy for a solitary renal mass. BJU international 120(4): 544-549	- Study does not contain a relevant outcome
Massari, Francesco, Di Nunno, Vincenzo, Gatto, Lidia et al. (2018) Should CARMENA Really Change our Attitude Towards Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma? A Systematic Review and Meta-Analysis Evaluating Cytoreductive Nephrectomy in the Era of Targeted Therapy. Targeted oncology 13(6): 705-714	- Mixed population of SACT pre/post non-pharmacological regimens
Masson-Lecomte, Alexandra, Bensalah, Karim, Seringe, Elise et al. (2013) A prospective comparison of surgical and pathological outcomes obtained after robot-assisted or pure laparoscopic partial nephrectomy in moderate to complex renal tumours: results from a French multicentre collaborative study. BJU international 111(2): 256-63	- Exclude - For review C. Proportion of patients stage T3 < 90%
Masson-Lecomte, Alexandra, Yates, David R, Hupertan, Vincent et al. (2013) A prospective comparison of the pathologic and surgical outcomes obtained after elective treatment of renal cell carcinoma by open or robot-assisted partial nephrectomy. Urologic oncology 31(6): 924-9	- There is no information on cT or pT stage
Mastroianni, R., Chiacchio, G., Perpepaj, L. et al. (2024) Comparison of Perioperative, Functional, and Oncologic Outcomes of Open vs. Robot-Assisted Off-Clamp Partial Nephrectomy: A Propensity Scored Match Analysis. Sensors (Basel, Switzerland) 24(9)	- Exclude review C- Study included only patients T1-T2
Mathieu, Romain, Pignot, Geraldine, Ingles, Alexandre et al. (2015) Nephrectomy improves overall survival in patients with metastatic renal cell carcinoma in cases of favorable MSKCC or ECOG prognostic features. Urologic oncology 33(8): 339e9-15	- Mixed population of SACT pre/post non-pharmacological regimens
May, D.N., Hill, H., Matrana, M.R. et al. (2021) A Contemporary Analysis of the 30-day Morbidity	- Comparator in study does not match that specified in protocol

Study	Reason
and Mortality Associated With Cytoreductive Nephrectomy. Urology 147: 186-191	
Mearini, Luigi, Nunzi, Elisabetta, Vianello, Alberto et al. (2016) Margin and complication rates in clampless partial nephrectomy: a comparison of open, laparoscopic and robotic surgeries. Journal of robotic surgery 10(2): 135-44	- There is no information on cT or pT stage
Mehra, Ketan, Manikandan, Ramanitharan, Dorairajan, Lalgudi Narayanan et al. (2019) Trifecta Outcomes in Open, Laparoscopy or Robotic Partial Nephrectomy: Does the Surgical Approach Matter?. Journal of kidney cancer and VHL 6(1): 8-12	- Non-OECD country - There is no information on cT or pT stage
Mennitto, A, Verzoni, E, Cognetti, F et al. (2021) Radical metastasectomy followed by sorafenib versus observation in patients withclear cell renal cell carcinoma: extended follow -up of efficacy results from the randomized phase II RESORT trial. Expert review of clinical pharmacology 14(2): 261-268	- Comparator in study does not match that specified in protocol *Compares patients with metastatic rcc treated with sorafenib vs. observation-alone after the radical surgery of metastases*
Mershon, J Patrick; Tuong, Mei N; Schenkman, Noah S (2020) Thermal ablation of the small renal mass: a critical analysis of current literature. Minerva urologica e nefrologica = The Italian journal of urology and nephrology 72(2): 123-134	- More recent systematic review included that covers the same topic
Metcalf, Meredith R, Cheaib, Joseph G, Biles, Michael J et al. (2021) Outcomes of Active Surveillance for Young Patients with Small Renal Masses: Prospective Data from the DISSRM Registry. The Journal of urology 205(5): 1286-1293	- Comparator in study does not match that specified in protocol *Surgery and cryoablation combined*
Metcalf, Meredith R, Pena, Vanessa N, Cheaib, Joseph G et al. (2022) Disparities in the Treatment and Survival of Metastatic Renal Cell Carcinoma. Urology 165: 89-97	- Mixed population of SACT pre/post non-pharmacological regimens
Michalak, M., Kopczynska, A., Antczak, A. et al. (2024) Outcomes of treatment, laboratory results, adverse effects, and tolerability of cancer treatment in patients with metastatic renal cell carcinoma treated with ipilimumab and nivolumab after cytoreductive nephrectomy. Nowotwory 74(6): 344	- Data not reported in an extractable format *Data for PFS was reported as mean and range only*

Study	Reason
Michalak, M., Tomczak, P., Milecki, T. et al. (2024) Outcomes of treatment, laboratory results, adverse effects, and tolerability of cancer treatment in patients with metastatic renal-cell carcinoma treated with sunitinib after cytoreductive nephrectomy. Nowotwory 74(2): 105	- Exclude - assessed outcome is out of scope
Miller, Brady L, Mankowski Gettle, Lori, Van Roo, Jason R et al. (2018) Comparative Analysis of Surgery, Thermal Ablation, and Active Surveillance for Renal Oncocytic Neoplasms. Urology 112: 92-97	- Does not contain a population of people with kidney cancer
Miller, Jacob A, Balagamwala, Ehsan H, Angelov, Lilyana et al. (2016) Spine stereotactic radiosurgery with concurrent tyrosine kinase inhibitors for metastatic renal cell carcinoma. Journal of neurosurgery. Spine 25(6): 766-774	- Conference abstract
Minervini, Andrea, Vittori, Gianni, Antonelli, Alessandro et al. (2014) Open versus robotic-assisted partial nephrectomy: a multicenter comparison study of perioperative results and complications. World journal of urology 32(1): 287-93	- Exclude - For review C. Proportion of patients stage T3 < 90%
Mir, Maria Carmen, Derweesh, Ithaar, Porpiglia, Francesco et al. (2017) Partial Nephrectomy Versus Radical Nephrectomy for Clinical T1b and T2 Renal Tumors: A Systematic Review and Meta-analysis of Comparative Studies. European urology 71(4): 606-617	- Systematic review used as source of primary studies
Mitchell, Christopher R, Atwell, Thomas D, Weisbrod, Adam J et al. (2011) Renal function outcomes in patients treated with partial nephrectomy versus percutaneous ablation for renal tumors in a solitary kidney. The Journal of urology 186(5): 1786-90	- Study does not contain a relevant outcome *eGFR during postop period only*
Mittal, Abhenil, Al-Ezzi, Esmail, Li, Xuan et al. (2023) The role of cytoreductive nephrectomy and systemic therapy in the management of tumour thrombus in patients with metastatic renal cell carcinoma. British journal of cancer 128(10): 1888-1896	- Mixed population of SACT pre/post non-pharmacological regimens
Miyake, Hideaki, Hinata, Nobuyuki, Imai, Satoshi et al. (2015) Partial nephrectomy for hilar tumors: comparison of conventional open and robot-assisted approaches. International journal of clinical oncology 20(4): 808-13	- There is no information on cT or pT stage

Study	Reason
Mo, Cheng-Qiang, Yu, Zhou, Tan, Wu-Lin et al. (2014) Comparison between laparoscopic partial nephrectomy and laparoscopic ablation therapy: a meta-analysis. Minimally invasive therapy & allied technologies : MITAT : official journal of the Society for Minimally Invasive Therapy 23(6): 317-25	- More recent systematic review included that covers the same topic
Monda, S.; Lara, P.N.; Gulati, S. (2024) Post-Metastasectomy Adjuvant Therapy in Patients with Renal Cell Carcinoma: A Systematic Review. Kidney Cancer 8(1): 115	- Comparator in study does not match that specified in protocol
Mori, Keiichiro, Quhal, Fahad, Yanagisawa, Takafumi et al. (2022) The effect of immune checkpoint inhibitor combination therapies in metastatic renal cell carcinoma patients with and without previous cytoreductive nephrectomy: A systematic review and meta-analysis. International immunopharmacology 108: 108720	- Mixed population of SACT pre/post non-pharmacological regimens
Morkos, John, Porosnicu Rodriguez, Kori A, Zhou, Alice et al. (2020) Percutaneous Cryoablation for Stage 1 Renal Cell Carcinoma: Outcomes from a 10-year Prospective Study and Comparison with Matched Cohorts from the National Cancer Database. Radiology 296(2): 452-459	- Secondary publication of an included study that does not provide any additional relevant information
Muhlbauer, Julia, de Gilde, Johannes, Mueller-Steinhardt, Michael et al. (2020) Perioperative Blood Transfusion Is a Predictor of Acute and Chronic Renal Function Deterioration after Partial and Radical Nephrectomy for Renal Cell Carcinoma. Urologia internationalis 104(910): 775-780	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Muhlbauer, Julia, Kowalewski, Karl-Friedrich, Walach, Margarete T et al. (2020) Partial nephrectomy preserves renal function without increasing the risk of complications compared with radical nephrectomy for renal cell carcinomas of stages pT2-3a. International journal of urology : official journal of the Japanese Urological Association 27(10): 906-913	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Nakada, S Y, Fadden, P, Jarrard, D F et al. (2001) Hand-assisted laparoscopic radical nephrectomy: comparison to open radical nephrectomy. Urology 58(4): 517-20	- Exclude , review C. Patients with localised tumour

Study	Reason
Nandanan, N., Veccia, A., Antonelli, A. et al. (2020) Outcomes and predictors of benign histology in patients undergoing robotic partial or radical nephrectomy for renal masses: A multicenter study. Central European Journal of Urology 73(1): 33-38	- Study does not contain a relevant outcome
Nason, Gregory J, Walsh, Leon G, Redmond, Ciaran E et al. (2015) Comparative effectiveness of adrenal sparing radical nephrectomy and non-adrenal sparing radical nephrectomy in clear cell renal cell carcinoma: Observational study of survival outcomes. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 9(910): e583-8	- Comparator in study does not match that specified in protocol
Nayak, J.G., Patel, P., Saarela, O. et al. (2016) Pathological Upstaging of Clinical T1 to Pathological T3a Renal Cell Carcinoma: A Multi-institutional Analysis of Short-term Outcomes. Urology 94: 154-160	- Primary study covered fully by an included systematic review
Nguyen, D.P., Vertosick, E.A., Corradi, R.B. et al. (2016) Histological subtype of renal cell carcinoma significantly affects survival in the era of partial nephrectomy. Urologic Oncology: Seminars and Original Investigations 34(6): e1-259	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Nian, Xinwen, Ye, Huamao, Zhang, Wei et al. (2022) Propensity-matched pair analysis of safety and efficacy between laparoscopic and open radical nephrectomy for the treatment of large renal masses (>10 cm): a retrospective cohort study. Translational andrology and urology 11(8): 1148-1156	- Exclude, review C. Study included only patients T1-T2
Nicaise, Edouard, Feldman, Adam S, Gusev, Andrew et al. (2024) A contemporary comparison of laparoscopic versus open partial nephrectomy for renal cell carcinoma. BMC urology 24(1): 58	- Exclude, review C - Study included only patients T1-T2
Nowak, Lukasz, Janczak, Dawid, Laszkiewicz, Jan et al. (2024) Clinical and Oncological Outcomes Following Percutaneous Cryoablation vs. Partial Nephrectomy for Clinical T1 Renal Tumours: Systematic Review and Meta-Analysis. Cancers 16(6)	- Systematic review used as source of primary studies
Nunez Bragayrac, Luciano, Hoffmeyer, Jan, Abbotoy, Daniel et al. (2016) Minimally invasive	- Comparator in study does not match that specified in protocol

Study	Reason
cytoreductive nephrectomy: a multi-institutional experience. World journal of urology 34(12): 1651-1656	*No information about SACT*
O'Malley, Rebecca L, Berger, Aaron D, Kanofsky, Jamie A et al. (2007) A matched-cohort comparison of laparoscopic cryoablation and laparoscopic partial nephrectomy for treating renal masses. BJU international 99(2): 395-8	- Study published before included SR/s for the outcome/s reported
Ocak, Birol, Sahin, Ahmet Bilgehan, Erturk, Ismail et al. (2024) Can Cytoreductive Nephrectomy Improve Outcomes of Nivolumab Treatment in Patients with Metastatic Clear-Cell Renal Carcinoma?. Current oncology (Toronto, Ont.) 31(9): 5195-5205	- Data not reported in an extractable format *Only median (95% CI) OS has been reported. Other data is time to treatment discontinuation for systemic treatments which is out of scope for this review.*
Oh, Jong Jin, Byun, Seoksoo, Hong, Sung Kyu et al. (2014) Comparison of robotic and open partial nephrectomy: Single-surgeon matched cohort study. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 8(78): e471-5	- Exclude - For review C. Proportion of patients stage T3 < 90%
Ohno, Y., Nakashima, J., Ohori, M. et al. (2014) Clinical variables for predicting metastatic renal cell carcinoma patients who might not benefit from cytoreductive nephrectomy: Neutrophil-to-lymphocyte ratio and performance status. International Journal of Clinical Oncology 19(1): 139-145	- Mixed population of SACT pre/post non-pharmacological regimens *Unclear about the SACT treatment or any other treatment in no CN group*
Okita, Kazutaka, Hatakeyama, Shingo, Naito, Sei et al. (2021) External validation of the REMARCC model for the selection of cytoreductive nephrectomy in patients with primary metastatic renal cell carcinoma: A multicenter retrospective study. Urologic oncology 39(12): 836e11-836e17	- Comparator in study does not match that specified in protocol *Study compares CN vs SACT. Combines upfront and deferred CN participants into one CN arm. No subgroup results reported*
Olweny, Ephrem O, Park, Samuel K, Tan, Yung K et al. (2012) Radiofrequency ablation versus partial nephrectomy in patients with solitary clinical T1a renal cell carcinoma: comparable oncologic outcomes at a minimum of 5 years of follow-up. European urology 61(6): 1156-61	- Primary study covered fully by an included systematic review
Onal, Cem, Oymak, Ezgi, Guler, Ozan Cem et al. (2023) Stereotactic body radiotherapy and tyrosine kinase inhibitors in patients with oligometastatic renal cell carcinoma: a multi-institutional study. Strahlentherapie und	- Review H - SABR exclude - Mixed population of SACT pre/post non-pharmacological regimens

Study	Reason
Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al] 199(5): 456-464	
Onishi, Takehisa, Nishikawa, Kouhei, Hasegawa, Yoshihiro et al. (2007) Assessment of health-related quality of life after radiofrequency ablation or laparoscopic surgery for small renal cell carcinoma: a prospective study with medical outcomes Study 36-Item Health Survey (SF-36). Japanese journal of clinical oncology 37(10): 750-4	- Study does not contain a relevant outcome *HRQoL reported as SF36*
Ontario, Health (2023) Robotic-assisted partial nephrectomy for kidney cancer.	- Exclude - wrong population *Population too broad*
Pahouja, Gaurav, Sweigert, Sarah E, Sweigert, Patrick J et al. (2022) Does size matter? Comparing robotic versus open radical nephrectomy for very large renal masses. Urologic oncology 40(10): 456e1-456e7	- Exclude - For review C. Proportion of patients stage T3 < 90%
Palacios, Diego Aguilar, Zabor, Emily C, Munoz-Lopez, Carlos et al. (2021) Does Reduced Renal Function Predispose to Cancer-specific Mortality from Renal Cell Carcinoma?. European urology 79(6): 774-780	- Data not reported in an extractable format *No denominators for recurrence data*
Palumbo, Carlotta, Mistretta, Francesco A, Knipper, Sophie et al. (2020) Contemporary Cytoreductive Nephrectomy Provides Survival Benefit in Clear-cell Metastatic Renal Cell Carcinoma. Clinical genitourinary cancer 18(6): e730-e738	- Mixed population of SACT pre/post non-pharmacological regimens
Pan, Xiu-Wu, Cui, Xin-Ming, Huang, Hai et al. (2015) Radiofrequency ablation versus partial nephrectomy for treatment of renal masses: A systematic review and meta-analysis. The Kaohsiung journal of medical sciences 31(12): 649-58	- More recent systematic review included that covers the same topic
Panian, Justine, Saidian, Ava, Hakimi, Kevin et al. (2023) Pathological Outcomes of Patients With Advanced Renal Cell Carcinoma Who Receive Nephrectomy Following Immunotherapy. The oncologist	- Not a relevant study design
Panumatrassamee, Kamol, Autorino, Riccardo, Laydner, Humberto et al. (2013) Robotic versus laparoscopic partial nephrectomy for tumor in a solitary kidney: a single institution comparative analysis. International journal of urology : official	- Exclude - For review C. Proportion of patients stage T3 < 90%

Study	Reason
journal of the Japanese Urological Association 20(5): 484-91	
Papadopoulou, Ariadni, Campain, Nicholas, Abu-Ghanem, Yasmin et al. (2024) Not-so-simple nephrectomy: Comparative analysis of radical and simple nephrectomy in a high-volume tertiary referral center. International journal of urology : official journal of the Japanese Urological Association 31(2): 160-168	- Comparator in study does not match that specified in protocol *Comparator is people who had simple nephrectomy; people who had partial nephrectomy were excluded.*
Patel, Hiten D, Kates, Max, Pierorazio, Phillip M et al. (2014) Survival after diagnosis of localized T1a kidney cancer: current population-based practice of surgery and nonsurgical management. Urology 83(1): 126-32	- Study does not contain a relevant intervention *Not clearly active surveillance*
Patel, Hiten D, Riffon, Mark F, Joice, Gregory A et al. (2016) A Prospective, Comparative Study of Quality of Life among Patients with Small Renal Masses Choosing Active Surveillance and Primary Intervention. The Journal of urology 196(5): 1356-1362	- Study does not contain a relevant outcome *QoL reported as SF12*
Patel, Sunil H, Uzzo, Robert G, Larcher, Alessandro et al. (2020) Oncologic and Functional Outcomes of Radical and Partial Nephrectomy in pT3a Pathologically Upstaged Renal Cell Carcinoma: A Multi-institutional Analysis. Clinical genitourinary cancer 18(6): e723-e729	- Comparator in study does not match that specified in protocol *PN vs RN*
Patton, Michael W, Salevitz, Daniel A, Tyson, Mark D 2nd et al. (2016) Robot-assisted partial nephrectomy for complex renal masses. Journal of robotic surgery 10(1): 27-31	- There is no information on cT or pT stage
Pecoraro, A., Roussel, E., Amparore, D. et al. (2023) New-onset Chronic Kidney Disease After Surgery for Localised Renal Masses in Patients with Two Kidneys and Preserved Renal Function: A Contemporary Multicentre Study. European Urology Open Science 52: 100-108	- Data not reported in an extractable format *No information on participant split between I and C, or baseline characteristics by intervention.*
Pecoraro, A, Amparore, D, Manfredi, M et al. (2022) Partial vs. radical nephrectomy in non-metastatic pT3a kidney cancer patients: a population-based study. Minerva urology and nephrology 74(4): 445-451	- Comparator in study does not match that specified in protocol *Compares PN vs RN in T3 tumours. Not applicable for review C.*
Peng, B, Zheng, J-H, Xu, D-F et al. (2006) Retroperitoneal laparoscopic nephrectomy and open nephrectomy for radical treatment of renal	- Study not reported in English

Study	Reason
cell carcinoma: a comparison of clinical outcomes. Academic journal of second military medical university 27(11): 1167-1169	
Peng, Ding, He, Zhi-Song, Li, Xue-Song et al. (2017) Partial nephrectomy for T3aN0M0 renal cell carcinoma: shall we step forward?. International braz j urol : official journal of the Brazilian Society of Urology 43(5): 849-856	- Non-OECD country - Comparator in study does not match that specified in protocol *Compares PN vs RN in T3 tumours. Not applicable for review C.*
Peng, Jonathan; Lalani, Aly-Khan; Swaminath, Anand (2021) Cytoreductive stereotactic body radiotherapy (SBRT) and combination SBRT with immune checkpoint inhibitors in metastatic renal cell carcinoma. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 15(8): 281-286	- Systematic review with single arm studies included only
Petrelli, Fausto, Coinu, Andrea, Vavassori, Ivano et al. (2016) Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma Treated With Targeted Therapies: A Systematic Review With a Meta-Analysis. Clinical genitourinary cancer 14(6): 465-472	- Exclude - Result reported in the most updated MA
Petros, Firas G, Venkatesan, Aradhana M, Kaya, Diana et al. (2019) Conditional survival of patients with small renal masses undergoing active surveillance. BJU international 123(3): 447-455	- Data not reported in an extractable format *Insufficient information about comparator arm to include*
Peyronnet, Benoit, Seisen, Thomas, Oger, Emmanuel et al. (2016) Comparison of 1800 Robotic and Open Partial Nephrectomies for Renal Tumors. Annals of surgical oncology 23(13): 4277-4283	- There is no information on cT or pT stage
Piening, A., Al-Hammadi, N., Dombrowski, J. et al. (2023) Survival in Metastatic Renal Cell Carcinoma Treated With Immunotherapy and Stereotactic Radiation Therapy or Immunotherapy Alone: A National Cancer Database Analysis. Advances in Radiation Oncology 8(5): 101238	- Mixed population of SACT pre/post non-pharmacological regimens *Combines participants receiving SACT and conventional radiotherapy in a single arm and compares it to SRT*
Pierorazio, Phillip M, Johnson, Michael H, Ball, Mark W et al. (2015) Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. European urology 68(3): 408-15	- Comparator in study does not match that specified in protocol *Does not separate ablation and nephrectomy in comparator group*

Study	Reason
Pierorazio, Phillip M, Johnson, Michael H, Patel, Hiten D et al. (2016) Management of Renal Masses and Localized Renal Cancer: Systematic Review and Meta-Analysis. The Journal of urology 196(4): 989-99	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*
Pignot, Geraldine, Margue, Gaelle, Bigot, Pierre et al. (2025) The effect of tumor downsizing on surgical complexity during nephrectomy after immune checkpoint inhibitors for metastatic renal cell carcinoma. World journal of urology 43(1): 54	- Study did not compare the interventions of interest
Pignot, Geraldine, Mejean, Arnaud, Bernhard, Jean-Christophe et al. (2015) The use of partial nephrectomy: results from a contemporary national prospective multicenter study. World journal of urology 33(1): 33-40	- Does not contain a population of people with kidney cancer *population has kidney cancer but >10% of participants have stage 3 or higher*
Pignot, Geraldine, Thiery-Vuillemin, Antoine, Albiges, Laurence et al. (2022) Oncological Outcomes of Delayed Nephrectomy After Optimal Response to Immune Checkpoint Inhibitors for Metastatic Renal Cell Carcinoma. European urology oncology 5(5): 577-584	- Comparator in study does not match that specified in protocol - Study does not contain a relevant intervention
Poinas, G, Long, JA, Rébillard, X et al. (2018) [Place of partial nephrectomy assisted by robot: Review of the literature at the time of a request for a specific nomenclature]. Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie 28(16): 890-899	- Study not reported in English
Posa, A., Lancellotta, V., Paoletti, F. et al. (2022) The Role of Focal Approach as Alternative to Nephron-Sparing Surgery in the Treatment of Stage I Cancer in Renal Graft: Results of a Systematic Review. Turk Onkoloji Dergisi 37(3): 351-360	- More recent systematic review included that covers the same topic *kidney graft patients only*
Prata, F., Ragusa, A., Tedesco, F. et al. (2024) Trifecta Outcomes of Robot-Assisted Partial Nephrectomy Using the New HugoTM RAS System Versus Laparoscopic Partial Nephrectomy. Journal of Clinical Medicine 13(7): 2138	- Exclude - For review C. Proportion of patients stage T3 < 90%
Prins, Fieke M, Kerkmeijer, Linda G W, Pronk, Anne A et al. (2017) Renal Cell Carcinoma: Alternative Nephron-Sparing Treatment Options for Small Renal Masses, a Systematic Review. Journal of endourology 31(10): 963-975	- More recent systematic review included that covers the same topic

Study	Reason
Procopio, Giuseppe, Apollonio, Giulia, Cognetti, Francesco et al. (2019) Sorafenib Versus Observation Following Radical Metastasectomy for Clear-cell Renal Cell Carcinoma: Results from the Phase 2 Randomized Open-label RESORT Study. European urology oncology 2(6): 699-707	- Comparator in study does not match that specified in protocol *Compares patients with metastatic rcc treated with sorafenib vs. observation-alone after the radical surgery of metastases*
Pyrgidis, N., Schulz, G.B., Stief, C. et al. (2024) Surgical Trends and Complications in Partial and Radical Nephrectomy: Results from the GRAND Study. Cancers 16(1): 97	- Data not reported in an extractable format *no info on tumour stage (see highlighted text on page 9)study reports length of hospital stay (table 3)we could include and downgrade for applicability To exclude - as there is no information on tumour characteristics*
Qi, Nienie, Wu, Pengjie, Chen, Jinchao et al. (2017) Cytoreductive nephrectomy with thrombectomy before targeted therapy improves survival for metastatic renal cell carcinoma with venous tumor thrombus: a single-center experience. World journal of surgical oncology 15(1): 4	- Study does not contain a relevant intervention
Qu, Hongchen; Wang, Kai; Hu, Bin (2023) Meta analysis of clinical prognosis of radiofrequency ablation versus partial nephrectomy in the treatment of early renal cell carcinoma. Frontiers in oncology 13: 1105877	- Systematic review used as source of primary studies *Sources insufficient*
Qu, Hongchen; Wang, Kai; Hu, Bin (2024) Meta-analysis of clinical outcomes of robot-assisted partial nephrectomy and classical open partial nephrectomy. International journal of surgery (London, England) 110(10): 6268-6281	- Exclude - review C. Patients with localised tumour
Raman, Jay D, Raj, Ganesh V, Lucas, Steven M et al. (2010) Renal functional outcomes for tumours in a solitary kidney managed by ablative or extirpative techniques. BJU international 105(4): 496-500	- Study published before included SR/s for the outcome/s reported
Reese, Stephen W, Eismann, Lennert, White, Charlie et al. (2023) Surgical outcomes of cytoreductive nephrectomy in patients receiving systemic immunotherapy for advanced renal cell carcinoma. Urologic oncology	- Comparator in study does not match that specified in protocol
Reifsnyder, Jennifer E, Ramasamy, Ranjith, Ng, Casey K et al. (2012) Laparoscopic and open partial nephrectomy: complication comparison using the Clavien system. JSLS : Journal of the Society of Laparoendoscopic Surgeons 16(1): 38-44	- There is no information on cT or pT stage

Study	Reason
Ricciardulli, Stefano, Ding, Qiang, Zhang, Xu et al. (2015) Evaluation of laparoscopic vs robotic partial nephrectomy using the margin, ischemia and complications score system: a retrospective single center analysis. Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica 87(1): 49-55	- Exclude, review C - Study included only patients T1-T2
Richey, S L, Culp, S H, Jonasch, E et al. (2011) Outcome of patients with metastatic renal cell carcinoma treated with targeted therapy without cytoreductive nephrectomy. Annals of oncology : official journal of the European Society for Medical Oncology 22(5): 1048-1053	- Comparator in study does not match that specified in protocol *Compares targeted therapy with chemotherapy and other types of SACT*
Rim, C.H., Cho, W.K., Lee, J.H. et al. (2022) Role of Local Treatment for Oligometastasis: A Comparability-Based Meta-Analysis. Cancer Research and Treatment 54(4): 953-969	- Exclude - wrong population - Exclude - Intervention is out of scope
Rini, Brian I and Campbell, Steven C (2007) The evolving role of surgery for advanced renal cell carcinoma in the era of molecular targeted therapy. The Journal of urology 177(6): 1978-84	- Review article but not a systematic review
Rivero, J Ricardo, De La Cerda, Jose 3rd, Wang, Hanzhang et al. (2018) Partial Nephrectomy versus Thermal Ablation for Clinical Stage T1 Renal Masses: Systematic Review and Meta-Analysis of More than 3,900 Patients. Journal of vascular and interventional radiology : JVIR 29(1): 18-29	- More recent systematic review included that covers the same topic
Roaldsen, Marius, Lohne, Vetle, Stenberg, Thor Allan et al. (2024) Comparing open and robot-assisted partial nephrectomy - a single institution report. BMC urology 24(1): 197	- Exclude, review C. Study included only patients T1-T2
Roussel, Eduard, Laenen, Annouschka, Bhindi, Bimal et al. (2023) Predicting short- and long-term renal function following partial and radical nephrectomy. Urologic oncology 41(2): 110e1-110e6	- Study does not contain a relevant outcome
Roussel, Eduard, Verbiest, Annelies, Milenkovic, Uros et al. (2020) Too good for CARMENA: criteria associated with long systemic therapy free intervals post cytoreductive nephrectomy for metastatic clear cell renal cell carcinoma. Scandinavian journal of urology 54(6): 493-499	- Study does not contain a relevant outcome

Study	Reason
Russo, P. (2009) Radical nephrectomy with and without lymph node dissection: Final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. Blom JH, van Poppel H, Marechal JM, Jacqmin D, Schroder FH, de Prijck L, Sylvester R, EORTC Genitourinary Tract Cancer Group, St. Franciscus Gasthuis, Rotterdam, The Netherlands. Urologic Oncology: Seminars and Original Investigations 27(1): 102	- Conference abstract
Russo, P., Blum, K.A., Weng, S. et al. (2022) Outcomes for Atypical Tumor Recurrences Following Minimally Invasive Kidney Cancer Operations. European Urology Open Science 40: 125-132	- Does not contain a population of people with kidney cancer *All participants were treated for recurrence after partial or radical nephrectomy*
Saeed, S., Shah, S.R., Najeebullah et al. (2024) THE ROLE OF NEPHRON-SPARING SURGERY IN THE MANAGEMENT OF SMALL RENAL MASSES COMPARING THE ONCOLOGICAL OUTCOMES, RENAL FUNCTION PRESERVATION, AND COMPLICATION RATES OF PARTIAL NEPHRECTOMY VERSUS RADICAL NEPHRECTOMY. Journal of Population Therapeutics and Clinical Pharmacology 31(9): 981	- Non-OECD country
Sandbergen, Laura, Spriensma, Alette S, de la Rosette, Jean J et al. (2020) Health-related quality of life in localized renal masses: A matter of sparing nephrons or minimizing the incision?. Urologic oncology 38(2): 43e1-43e11	- Study does not contain a relevant outcome *QoL as SF-36*
Schernuk, Jordan, Garcia Marchinena, Patricio A, Carminatti, Tomas et al. (2023) Renal Cell Carcinoma with Venous Extension: Safety of Laparoscopic Surgery for Thrombus Levels I-IIIa. Journal of endourology 37(7): 786-792	- Comparator in study does not match that specified in protocol
Schiff, Jonathan D, Palese, Michael, Vaughan, E Darracott Jr et al. (2005) Laparoscopic vs open partial nephrectomy in consecutive patients: the Cornell experience. BJU international 96(6): 811-4	- There is no information on cT or pT stage
Scosyrev, Emil, Messing, Edward M, Sylvester, Richard et al. (2014) Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. European urology 65(2): 372-7	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason
Scosyrev, Emil, Wu, Kevin, Levey, Helen R et al. (2014) Overall Survival after Partial Versus Radical Nephrectomy for a Small Renal Mass: Systematic Review of Observational Studies. Urology practice 1(1): 27-34	- More recent systematic review included that covers the same topic
Selim, A.M., Zaghloul, A.S., Aboulkassem, H.A. et al. (2020) Minimally invasive approach in surgical management of renal neoplasms national cancer institute experience. Open Access Macedonian Journal of Medical Sciences 8(b): 1071-1076	- Study does not contain a relevant intervention *Laparoscopic & robotic compared to open nephrectomy irrespective of being partial or radical*
Shah, Paras H, Leibovich, Bradley C, Van Houten, Holly et al. (2019) Association of Partial versus Radical Nephrectomy with Subsequent Hypertension Risk Following Renal Tumor Resection. The Journal of urology 202(1): 69-75	- Primary study covered fully by an included systematic review
Shah, Paras H, Moreira, Daniel M, Patel, Vinay R et al. (2017) Partial Nephrectomy is Associated with Higher Risk of Relapse Compared with Radical Nephrectomy for Clinical Stage T1 Renal Cell Carcinoma Pathologically Up Staged to T3a. The Journal of urology 198(2): 289-296	- Comparator in study does not match that specified in protocol *Compares RN and PN for upstaged T3 tumours.*
Sharma, Gopal, Sharma, Aditya Prakash, Tyagi, Shantanu et al. (2022) Robot-assisted partial nephrectomy for moderate to highly complex renal masses. A systematic review and meta-analysis. Indian journal of urology : IJU : journal of the Urological Society of India 38(3): 174-183	- Exclude - For review C. Proportion of patients stage T3 < 90%
Shaw, Greg L, Hussain, Mahreen, Nair, Rajesh et al. (2012) Performing cytoreductive nephrectomy following targeted sunitinib therapy for metastatic renal cell carcinoma: a surgical perspective. Urologia internationalis 89(1): 83-8	- Comparator in study does not match that specified in protocol
Shchukin, D.V., Lesovoy, V.N., Garagatiy, I.A. et al. (2017) Comparative analysis of oncologic outcomes of radical nephrectomy and nephron-sparing surgery in patients with intravenous extension of tumor into the renal vein. New Armenian Medical Journal 11(2): 58-62	- Non-OECD country - Comparator in study does not match that specified in protocol *Comparing RN vs PN in locally advanced tumours*
Shemshaki, Hamidreza, Al-Mamari, Said Abdallah, Al-Hooti, Qais et al. (2022) Comparison of cytoreductive partial versus radical nephrectomy in metastatic renal cell carcinoma: To be on the horns of a dilemma. Urologia 89(2): 160-166	- Exclude - Intervention is out of scope

Study	Reason
Shen, Zhonghua, Xie, Linguo, Xie, Wanqin et al. (2016) The comparison of perioperative outcomes of robot-assisted and open partial nephrectomy: a systematic review and meta-analysis. World journal of surgical oncology 14(1): 220	- Exclude - For review C. Proportion of patients stage T3 < 90%
Shi, Xu, Feng, Dechao, Li, Dengxiong et al. (2021) The Role of Lymph Node Dissection for Non-Metastatic Renal Cell Carcinoma: An Updated Systematic Review and Meta-Analysis. Frontiers in oncology 11: 790381	- Exclude - For review C. Proportion of patients stage T3 < 90%
Shinohara, N, Harabayashi, T, Sato, S et al. (2001) Impact of nephron-sparing surgery on quality of life in patients with localized renal cell carcinoma. European urology 39(1): 114-9	- Data not reported in an extractable format
Shirotake, Suguru, Miyama, Y U, Baba, Yasutaka et al. (2022) Impact of Cytoreductive Nephrectomy Following Nivolumab Plus Ipilimumab Therapy for Patients With Advanced Renal Cell Carcinoma. Anticancer research 42(5): 2727-2735	- Study does not contain a relevant outcome - Not a relevant study design
Shvero, Asaf, Nativ, Ofer, Abu-Ghanem, Yasmin et al. (2018) Oncologic Outcomes of Partial Nephrectomy for Stage T3a Renal Cell Cancer. Clinical genitourinary cancer 16(3): e613-e617	- Comparator in study does not match that specified in protocol *Compared PN vs RN in locally advanced tumours*
Sidoti Abate, Marie Angela, Menold, Hanna Saskia, Neuberger, Manuel et al. (2024) Quality-of-life outcomes of the ROBOtic-assisted versus Conventional Open Partial nephrectomy (ROBOCOP) II trial. BJU international 134(3): 434-441	- Exclude - For review C. Proportion of patients stage T3 < 90%
Simhan, J., Smaldone, M.C., Tsai, K.J. et al. (2012) Perioperative outcomes of robotic and open partial nephrectomy for moderately and highly complex renal lesions. Journal of Urology 187(6): 2000-2004	- There is no information on cT or pT stage
Simone, Giuseppe, Tuderti, Gabriele, Anceschi, Umberto et al. (2017) Oncological outcomes of minimally invasive partial versus minimally invasive radical nephrectomy for cT1-2/N0/M0 clear cell renal cell carcinoma: a propensity score-matched analysis. World journal of urology 35(5): 789-794	- Data not reported in an extractable format
Siva, Shankar, Ali, Muhammad, Correa, Rohann J M et al. (2022) 5-year outcomes after	- Review article but not a systematic review

Study	Reason
stereotactic ablative body radiotherapy for primary renal cell carcinoma: an individual patient data meta-analysis from IROCK (the International Radiosurgery Consortium of the Kidney). The Lancet. Oncology 23(12): 1508-1516	
Siva, Shankar, Louie, Alexander V, Kotecha, Rupesh et al. (2024) Stereotactic body radiotherapy for primary renal cell carcinoma: a systematic review and practice guideline from the International Society of Stereotactic Radiosurgery (ISRS). The Lancet. Oncology 25(1): e18-e28	- Not a relevant study design *Single arm studies only*
Siva, Shankar, Pham, Daniel, Gill, Suki et al. (2012) A systematic review of stereotactic radiotherapy ablation for primary renal cell carcinoma. BJU international 110(11ptb): e737-43	- More recent systematic review included that covers the same topic
Soisrithong, C., Sirisreetreerux, P., Sangkum, P. et al. (2021) Comparative outcomes and predictive assessment of trifecta in open, laparoscopic, and robotic-assisted partial nephrectomy cases with renal cell carcinoma: A 10-year experience at ramathibodi hospital. Research and Reports in Urology 13: 425-435	- Non-OECD country - There is no information on cT or pT stage
Song, Y., Du, C.-X., Zhang, W. et al. (2016) Impact of cytoreductive nephrectomy on survival in patients with metastatic renal cell carcinoma treated by targeted therapy. Chinese Medical Journal 129(5): 530-535	- Data not reported in an extractable format *OS data reported as median and range*
Soomro, Naeem, Lecouturier, Jan, Stocken, Deborah D et al. (2017) Surveillance versus ablation for incidentally diagnosed small renal tumours: the SURAB feasibility RCT. Health technology assessment (Winchester, England) 21(81): 1-68	- Study does not contain a relevant outcome
Spaas, M, Sundahl, N, Rottey, S et al. (2021) Immuno-radiotherapy in solid tumors: preliminary results of the randomized phase 2 CHEERS trial. Radiotherapy and oncology 161: S490-S491	- Conference abstract
Spaas, Mathieu, Sundahl, Nora, Kruse, Vibeke et al. (2023) Checkpoint Inhibitors in Combination With Stereotactic Body Radiotherapy in Patients With Advanced Solid	- Review H - SABR exclude

Study	Reason
Tumors: The CHEERS Phase 2 Randomized Clinical Trial. JAMA oncology 9(9): 1205-1213	
Spiess, Philippe E and Fishman, Mayer N (2010) Cytoreductive nephrectomy vs medical therapy as initial treatment: a rational approach to the sequence question in metastatic renal cell carcinoma. Cancer control : journal of the Moffitt Cancer Center 17(4): 269-78	- Review article but not a systematic review
Sprenkle, Preston C, Power, Nicholas, Ghoneim, Tarek et al. (2012) Comparison of open and minimally invasive partial nephrectomy for renal tumors 4-7 centimeters. European urology 61(3): 593-9	- Exclude - For review C. Proportion of patients stage T3 < 90%
Stellato, M., Santini, D., Verzoni, E. et al. (2021) Impact of Previous Nephrectomy on Clinical Outcome of Metastatic Renal Carcinoma Treated With Immune-Oncology: A Real-World Study on Behalf of Meet-URO Group (MeetUro-7b). Frontiers in Oncology 11: 682449	- Not a relevant study design - Study does not contain a relevant intervention *Mixed CN and radical nephrectomy population*
Stenman, M, Sinclair, G, Paavola, P et al. (2018) Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005-2014. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 127(3): 501-506	- Comparator in study does not match that specified in protocol *Compares SRT with metastasectomy. Mixed SACT population*
Stern, Joshua M, Svatek, Robert, Park, Sangtae et al. (2007) Intermediate comparison of partial nephrectomy and radiofrequency ablation for clinical T1a renal tumours. BJU international 100(2): 287-90	- Primary study covered fully by an included systematic review
Steward, James E, Kern, Sean Q, Cheng, Liang et al. (2021) Clear cell papillary renal cell carcinoma: Characteristics and survival outcomes from a large single institutional series. Urologic oncology 39(6): 370e21-370e25	- Not a relevant study design
Stewart, Grant D, Ang, W Jensen, Laird, Alexander et al. (2012) The operative safety and oncological outcomes of laparoscopic nephrectomy for T3 renal cell cancer. BJU international 110(6): 884-90	- Not a relevant study design *Non-comparative study*
Stroup, Sean P, Palazzi, Kerrin, Kopp, Ryan P et al. (2012) RENAL nephrometry score is associated with operative approach for partial	- Exclude - For review C. Proportion of patients stage T3 < 90%

Study	Reason
nephrectomy and urine leak. Urology 80(1): 151-6	
Su, Jia-Rui, Zhu, Ding-Jun, Liang, Wu et al. (2012) Investigation on the indication of ipsilateral adrenalectomy in radical nephrectomy: a meta-analysis. Chinese medical journal 125(21): 3885-90	- Comparator in study does not match that specified in protocol *Adrenalectomy vs no adrenalectomy*
Suk-Ouichai, Chalairat, Tanaka, Hajime, Wang, Yanbo et al. (2019) Renal Cancer Surgery in Patients without Preexisting Chronic Kidney Disease-Is There a Survival Benefit for Partial Nephrectomy?. The Journal of urology 201(6): 1088-1096	- Data not reported in an extractable format *Stage of kidney cancer was not reported*
Sun, M, Abdollah, F, Shariat, S F et al. (2012) Propensity-score matched comparison of complications, blood transfusions, length of stay, and in-hospital mortality between open and laparoscopic partial nephrectomy: a national series. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 38(1): 80-7	- There is no information on cT or pT stage
Sun, Maxine, Becker, Andreas, Tian, Zhe et al. (2014) Management of localized kidney cancer: calculating cancer-specific mortality and competing risks of death for surgery and nonsurgical management. European urology 65(1): 235-41	- Study does not contain a relevant intervention *Non-surgical management is unclear*
Sun, Zi-Jun, Liu, Feng, Wei, Hai-Bin et al. (2023) Laparoscopic partial versus radical nephrectomy for localized renal cell carcinoma over 4 cm. Journal of cancer research and clinical oncology 149(20): 17837-17848	- Non-OECD country
Takagi, T., Kondo, T., Iizuka, J. et al. (2016) Comparison of survival rates in stage 1 renal cell carcinoma between partial nephrectomy and radical nephrectomy patients according to age distribution: A propensity score matching study. BJU International 117(6): e52-e59	- For review A. Study published before 2016 (search date for overall survival)
Takagi, Toshio, Kondo, Tsunenori, Omae, Kenji et al. (2016) Comparison of progression to end-stage renal disease requiring dialysis after partial or radical nephrectomy for renal cell carcinoma in patients with severe chronic kidney disease. International urology and nephrology 48(9): 1421-7	- Study does not contain a relevant outcome

Study	Reason
Takahara, K., Fukaya, K., Nukaya, T. et al. (2022) Perioperative and long-term functional outcomes of robot-assisted versus open partial nephrectomy: A single-center retrospective study of a Japanese cohort. Annals of Medicine and Surgery 75: 103482	- There is no information on cT or pT stage
Talenfeld, Adam D, Gennarelli, Renee L, Elkin, Elena B et al. (2018) Percutaneous Ablation Versus Partial and Radical Nephrectomy for T1a Renal Cancer: A Population-Based Analysis. Annals of internal medicine 169(2): 69-77	- Secondary publication of an included study that does not provide any additional relevant information *SEER database - covered by other included studies*
Tam, Andrew W, Kutikov, Alexander, Winoker, Jared S et al. (2022) Propensity-score matched oncological outcomes and patterns of recurrence following open and minimally-invasive partial nephrectomy for renal cell carcinoma. Urologic oncology 40(3): 111e19-111e25	- Exclude - For review C. Proportion of patients stage T3 < 90%
Tan, H.-J., Wolf Jr., J.S., Ye, Z. et al. (2011) Population-level comparative effectiveness of laparoscopic versus open radical nephrectomy for patients with kidney cancer. Cancer 117(18): 4184-4193	- Exclude - review C. Patients with localised tumour
Tan, Jo-Lynn, Frydenberg, Mark, Grummet, Jeremy et al. (2018) Comparison of perioperative, renal and oncologic outcomes in robotic-assisted versus open partial nephrectomy. ANZ journal of surgery 88(3): e194-e199	- Exclude - For review C. Proportion of patients stage T3 < 90%
Tang, Amber B, Lamaina, Margherita, Childers, Christopher P et al. (2021) Perioperative and Long-Term Outcomes of Robot-Assisted Partial Nephrectomy: A Systematic Review. The American surgeon 87(1): 21-29	- Exclude - For review C. Proportion of patients stage T3 < 90%
Tang, Kun, Yao, Weimin, Li, Heng et al. (2014) Laparoscopic renal cryoablation versus laparoscopic partial nephrectomy for the treatment of small renal masses: a systematic review and meta-analysis of comparative studies. Journal of laparoendoscopic & advanced surgical techniques. Part A 24(6): 403-10	- More recent systematic review included that covers the same topic
Tarkowska, M., Glowacka-Mrotek, I., Peterson, D. et al. (2023) Quality of life at 3 to 5 years after surgical treatment of renal cell carcinoma -	- Study does not contain a relevant outcome *Quality of life was measured with the WHOQOL-BREF questionnaire*

Study	Reason
a pilot cross-sectional study. Nowotwory 73(4): 201-212	
Tatsugami, Katsunori, Shinohara, Nobuo, Kondo, Tsunenori et al. (2015) Role of cytoreductive nephrectomy for Japanese patients with primary renal cell carcinoma in the cytokine and targeted therapy era. International journal of urology : official journal of the Japanese Urological Association 22(8): 736-40	- Mixed population of SACT pre/post non-pharmacological regimens
Teishima, J., Hara, T., Tobe, T. et al. (2023) The impact of primary region resection on the therapeutic outcome of combination regimens for metastatic renal cell carcinoma. Oncology Letters 26(5): 470	- Study does not contain a relevant outcome
Teishima, Jun, Goto, Keisuke, Sekino, Yohei et al. (2022) Prognostic model of upfront cytoreductive nephrectomy in patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors and/or targeted agents. International urology and nephrology 54(6): 1225-1232	- Data not reported in an extractable format
Teishima, Jun, Ohara, Shinya, Shinmei, Shunsuke et al. (2018) Normalization of C-reactive protein levels following cytoreductive nephrectomy in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors is associated with improved overall survival. Urologic oncology 36(7): 339e9-339e15	- Comparator in study does not match that specified in protocol
Thaidumrong, T. and Duangkae, S. (2018) Comparison of the outcomes of laparoscopic and open nephrectomy in Rajavithi hospital. Journal of the Medical Association of Thailand 101(2supplement2): 103-s108	- Non-OECD country - Exclude - For review C. Proportion of patients stage T3 < 90%
Thompson, R Houston, Atwell, Tom, Schmit, Grant et al. (2015) Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. European urology 67(2): 252-9	- Primary study covered fully by an included systematic review
Tian, J., Zeng, X., Wan, J. et al. (2022) Partial and Radical Nephrectomy Provides Equivalent Oncologic Outcomes in pT3a Renal Cell Carcinoma: A Population-Based Study. Frontiers in Oncology 11: 819098	- Comparator in study does not match that specified in protocol *Compares RN vs PN for upstaged T3 tumours*
Tobert, Conrad M; Riedinger, Christopher B; Lane, Brian R (2014) Do we know (or just	- Review article but not a systematic review

Study	Reason
believe) that partial nephrectomy leads to better survival than radical nephrectomy for renal cancer?. World journal of urology 32(3): 573-9	
Tsai, Sheng-Han, Tseng, Ping-Tao, Sherer, Benjamin A et al. (2019) Open versus robotic partial nephrectomy: Systematic review and meta-analysis of contemporary studies. The international journal of medical robotics + computer assisted surgery : MRCAS 15(1): e1963	- Exclude - For Review C. Proportion of patients stage T3 < 90%
Uhlig, A., Hahn, O., Strauss, A. et al. (2018) Treatment for Localized T1a Clear Cell Renal Cell Carcinoma: Survival Benefit for Cryosurgery and Thermal Ablation Compared to Deferred Therapy. CardioVascular and Interventional Radiology 41(2): 277-283	- Secondary publication of an included study that does not provide any additional relevant information *NCDB database - more recent studies from this database included*
Uhlig, Johannes, Kokabi, Nima, Xing, Minzhi et al. (2018) Ablation versus Resection for Stage 1A Renal Cell Carcinoma: National Variation in Clinical Management and Selected Outcomes. Radiology 288(3): 889-897	- Secondary publication of an included study that does not provide any additional relevant information
Uhlig, Johannes, Strauss, Arne, Rucker, Gerta et al. (2019) Partial nephrectomy versus ablative techniques for small renal masses: a systematic review and network meta-analysis. European radiology 29(3): 1293-1307	- More recent systematic review included that covers the same topic
Uprety, Dipesh, Bista, Amir, Smith, Angela L et al. (2018) Cytoreductive Nephrectomy in Elderly Patients with Metastatic Renal Cell Carcinoma in the Targeted Therapy Era. Anticancer research 38(5): 3013-3018	- Study does not contain a relevant intervention *No information about SACT* - Not a relevant study design *Case-control*
Van Poppel, Hein, Becker, Frank, Cadeddu, Jeffrey A et al. (2011) Treatment of localised renal cell carcinoma. European urology 60(4): 662-72	- Review article but not a systematic review
Vartolomei, Liliana, Cotrus, Andrei, Stanciu, Camelia et al. (2022) Quality of Life and Psychological Distress among Patients with Small Renal Masses. Journal of clinical medicine 11(14)	- Systematic review used as source of primary studies
Veccia, Alessandro, Dell'oglio, Paolo, Antonelli, Alessandro et al. (2020) Robotic partial nephrectomy versus radical nephrectomy in elderly patients with large renal masses.	- Data not reported in an extractable format *Data was not reported by stage of kidney cancer*

Study	Reason
Minerva urologica e nefrologica = The Italian journal of urology and nephrology 72(1): 99-108	
Veltri, Andrea, Gazzera, Carlo, Busso, Marco et al. (2014) T1a as the sole selection criterion for RFA of renal masses: randomized controlled trials versus surgery should not be postponed. Cardiovascular and interventional radiology 37(5): 1292-8	- Not a relevant study design *Noncomparative study*
Venkatramani, Vivek, Koru-Sengul, Tulay, Miao, Feng et al. (2018) A comparison of overall survival and perioperative outcomes between partial and radical nephrectomy for cT1b and cT2 renal cell carcinoma-Analysis of a national cancer registry. Urologic oncology 36(3): 90e9-90e14	- Superceded by Ristau
Verbiest, A., De Meerleer, G., Albersen, M. et al. (2018) Non-surgical ablative treatment of distant extracranial metastases for renal cell carcinoma: A systematic review. Kidney Cancer 2(1): 57-67	- Systematic review used as source of primary studies
Verbiest, A., Roussel, E., Tosco, L. et al. (2020) Long-Term Outcomes in Clear-Cell Renal Cell Carcinoma Patients Treated with Complete Metastasectomy. Kidney Cancer 4(4): 177-183	- Mixed population of SACT pre/post non-pharmacological regimens
Verzoni, Elena, Ratta, Raffaele, Grassi, Paolo et al. (2018) TARIBO trial: targeted therapy with or without nephrectomy in metastatic renal cell carcinoma: liquid biopsy for biomarkers discovery. Tumori 104(5): 401-405	- Not a relevant study design *Protocol for TARIBO trial. On going trial.*
Veys, Ralf, Abdollah, Firas, Briganti, Alberto et al. (2018) Oncological and functional efficacy of nephron-sparing surgery versus radical nephrectomy in renal cell carcinoma stages >=cT1b: a single institution, matched analysis. Central European journal of urology 71(1): 48-57	- Exclude - wrong population
Vilaseca, Antoni, Guglielmetti, Giuliano, Vertosick, Emily A et al. (2020) Value of Partial Nephrectomy for Renal Cortical Tumors of cT2 or Greater Stage: A Risk-benefit Analysis of Renal Function Preservation Versus Increased Postoperative Morbidity. European urology oncology 3(3): 365-371	- Comparator in study does not match that specified in protocol *Compares RN vs PN in locally advanced RCC*
Vitruk, Iurii, Voylenko, Oleg, Stakhovsky, Oleksandr et al. (2023) Advantages of organ-sparing treatment approaches in metastatic	- Comparator in study does not match that specified in protocol

Study	Reason
kidney cancer. Journal of cancer research and clinical oncology 149(7): 3131-3137	*Compares complete CN and partial CN. Inclusion criteria indicates all participants received SACT*
Wang, Agnes J and Bhayani, Sam B (2009) Robotic partial nephrectomy versus laparoscopic partial nephrectomy for renal cell carcinoma: single-surgeon analysis of >100 consecutive procedures. Urology 73(2): 306-10	- There is no information on cT or pT stage
Wang, Dong, Xiao, Zejun, Shou, Jianzhong et al. (2019) Comparison of Laparoscopy and Open Radical Nephrectomy of Renal Cell Cancer. Open medicine (Warsaw, Poland) 14: 392-397	- Exclude - For Review C. Proportion of patients stage T3 < 90%
Wang, Li, Li, Kun-Peng, Yin, Shan et al. (2023) Oncologic and perioperative outcomes of laparoscopic versus open radical nephrectomy for the treatment of renal tumor (> 7 cm): a systematic review and pooled analysis of comparative outcomes. World journal of surgical oncology 21(1): 35	- Exclude - For Review C. Proportion of patients stage T3 < 90%
Wang, Luke L, Yuen, Kit L, Saitta, Cesare et al. (2024) Comparison of outcomes of radical and partial nephrectomy for sarcomatoid renal cell carcinoma: analysis of the national cancer database. World journal of urology 42(1): 508	- Patients with sarcomatoid RCC and pT3 > 10% (61%)
Wang, Shangqian, Qin, Chao, Peng, Zhihang et al. (2014) Radiofrequency ablation versus partial nephrectomy for the treatment of clinical stage 1 renal masses: a systematic review and meta-analysis. Chinese medical journal 127(13): 2497-503	- More recent systematic review included that covers the same topic
Wang, Yubin, Ma, Xin, Huang, Qingbo et al. (2016) Comparison of robot-assisted and laparoscopic partial nephrectomy for complex renal tumours with a RENAL nephrometry score >=7: peri-operative and oncological outcomes. BJU international 117(1): 126-30	- Non-OECD country - Exclude - For Review C. Proportion of patients stage T3 < 90%
Wang, Yubin, Shao, Jinkai, Ma, Xin et al. (2017) Robotic and open partial nephrectomy for complex renal tumors: a matched-pair comparison with a long-term follow-up. World journal of urology 35(1): 73-80	- Non-OECD country - Exclude - For Review C. Proportion of patients stage T3 < 90%
Wang, Zheng, Wang, Ganggang, Xia, Qinghua et al. (2016) Partial nephrectomy vs. radical nephrectomy for renal tumors: A meta-analysis	- More recent systematic review included that covers the same topic

Study	Reason
of renal function and cardiovascular outcomes. Urologic oncology 34(12): 533e11-533e19	
Webb, C.M., Kamel, M., Eltahawy, E. et al. (2015) A comparative study of open, laparoscopic and robotic partial nephrectomy in obese patients. Urology Annals 7(2): 231-234	- There is no information on cT or pT stage
Wei, Xiyi, Ren, Xiaohan, Ding, Yichao et al. (2019) Comparative outcomes of radio frequency ablation versus partial nephrectomy for T1 renal tumors: a systematic review. Translational andrology and urology 8(6): 601-608	- More recent systematic review included that covers the same topic
Weight, Christopher J, Lythgoe, Casey, Unnikrishnan, Raman et al. (2011) Partial nephrectomy does not compromise survival in patients with pathologic upstaging to pT2/pT3 or high-grade renal tumors compared with radical nephrectomy. Urology 77(5): 1142-6	- Comparator in study does not match that specified in protocol *RN vs PN in upstaged T2/T3 tumours. Not applicable for Review C.*
Wen, Zhi, Wang, Li, Huang, Jing et al. (2023) Perioperative, functional, and oncologic outcomes after ablation or partial nephrectomy for solitary renal tumors: a systematic review and meta-analysis of comparative trials. Frontiers in oncology 13: 1202587	- Systematic review used as source of primary studies *Solitary kidney only*
Whitson, Jared M; Harris, Catherine R; Meng, Maxwell V (2012) Population-based comparative effectiveness of nephron-sparing surgery vs ablation for small renal masses. BJU international 110(10): 1438-1443	- Secondary publication of an included study that does not provide any additional relevant information *SEER database - more fully covered in another included study*
Wong, Ruby; Patel, Bijendra; Biyani, Chandra Shekhar (2023) Perioperative outcomes between laparoscopic versus open versus robotic partial nephrectomy: Current Review. Urologia: 3915603231211975	- Exclude - For Review C. Proportion of patients stage T3 < 90%
Wu, Jing, Chang, Joshua, Bai, Harrison X et al. (2019) A Comparison of Cryoablation with Heat-Based Thermal Ablation for Treatment of Clinical T1a Renal Cell Carcinoma: A National Cancer Database Study. Journal of vascular and interventional radiology : JVIR 30(7): 1027-1033e3	- Comparator in study does not match that specified in protocol *Compares cryoablation with thermal ablation*
Wu, Xiaorong, Chen, Wei, Huang, Jiwei et al. (2020) Zero ischemia laparoscopic microwave ablation assisted enucleation vs. laparoscopic partial nephrectomy in clinical T1a renal tumor:	- Study does not contain a relevant intervention *Microwave ablation group also had tumour enucleation*

Study	Reason
a randomized clinical trial. Translational cancer research 9(1): 194-202	
Wu, Z., Li, M., Liu, B. et al. (2014) Robotic versus open partial nephrectomy: A systematic review and meta-analysis. PLoS ONE 9(4): e94878	- There is no information on cT or pT stage
Wu, Zhenjie, Li, Mingmin, Qu, Le et al. (2014) A propensity-score matched comparison of perioperative and early renal functional outcomes of robotic versus open partial nephrectomy. PloS one 9(4): e94195	- Non-OECD country - There is no information on cT or pT stage
Wu, Zhenjie, Li, Mingmin, Song, Shangqing et al. (2015) Propensity-score matched analysis comparing robot-assisted with laparoscopic partial nephrectomy. BJU international 115(3): 437-45	- Non-OECD country - There is no information on cT or pT stage
Xia, Leilei, Wang, Xianjin, Xu, Tianyuan et al. (2017) Systematic Review and Meta-Analysis of Comparative Studies Reporting Perioperative Outcomes of Robot-Assisted Partial Nephrectomy Versus Open Partial Nephrectomy. Journal of endourology 31(9): 893-909	- Exclude - For Review C. Proportion of patients stage T3 < 90%
Xiao, W.-J., Zhu, Y., Dai, B. et al. (2015) Assessment of survival of patients with metastatic clear cell renal cell carcinoma after radical cytoreductive nephrectomy versus no surgery: a seer analysis. International braz j urol : official journal of the Brazilian Society of Urology 41(2): 288-295	- Mixed population of SACT pre/post non-pharmacological regimens
Xiaobing, Wu, Wentao, Gong, Guangxiang, Liu et al. (2017) Comparison of radiofrequency ablation and partial nephrectomy for tumor in a solitary kidney. BMC urology 17(1): 79	- Non-OECD country
Xu, Haozhe, Xing, Zhuo, Ai, Kai et al. (2024) Patients with high nuclear grade pT1-ccRCC are more suitable for radical nephrectomy than partial nephrectomy: a multicenter retrospective study using propensity score. World journal of surgical oncology 22(1): 24	- Non-OECD country
Xu, L. and Fan, W. (2020) Efficacy of sorafenib combined with radiofrequency ablation in renal cancer and its effects on immunity and inflammation in patients. Journal of B.U.ON. 25(1): 514-519	- Mixed population of SACT pre/post non-pharmacological regimens *No information about SACT in the arm treated with radiofrequency ablation*

Study	Reason
	- Study does not contain a relevant outcome
Yan, Shuai, Yang, Wei, Zhu, Cheng-Mei et al. (2019) Comparison among cryoablation, radiofrequency ablation, and partial nephrectomy for renal cell carcinomas sized smaller than 2 cm or sized 2-4 cm: A population-based study. Medicine 98(21): e15610	- Non-OECD country
Yang, Chao and Liao, Zhaolin (2018) Comparison of Radical Nephrectomy and Partial Nephrectomy for T1 Renal Cell Carcinoma: A Meta-Analysis. Urologia internationalis 101(2): 175-183	- Systematic review used as source of primary studies
Yang, Chia-Min, Chung, Hsiao-Jen, Huang, Yi-Hsiu et al. (2014) Standardized analysis of laparoscopic and robotic-assisted partial nephrectomy complications with Clavien classification. Journal of the Chinese Medical Association : JCMA 77(12): 637-41	- Non-OECD country - There is no information on cT or pT stage
Yang, Chuance, Wang, Zhenlong, Huang, Shanlong et al. (2018) Retroperitoneal Laparoscopic Partial Nephrectomy Versus Radical Nephrectomy for Clinical T1 Renal Hilar Tumor: Comparison of Perioperative Characteristics and Short-Term Functional and Oncologic Outcomes. Journal of laparoendoscopic & advanced surgical techniques. Part A 28(10): 1183-1187	- Non-OECD country
Yang, F.; Zhou, Q.; Xing, N. (2020) Comparison of survival and renal function between partial and radical laparoscopic nephrectomy for T1b renal cell carcinoma. Journal of Cancer Research and Clinical Oncology 146(1): 261-272	- Non-OECD country
Yang, Quancheng, Meng, Fanzheng, Li, Kai et al. (2015) Safety and Efficacy of Thermal Ablation for Small Renal Masses in Solitary Kidney: Evidence from Meta-Analysis of Comparative Studies. PloS one 10(6): e0131290	- More recent systematic review included that covers the same topic
Yang, Yong (2020) Partial Versus Radical Nephrectomy in Patients with Renal Cell Carcinoma: A Systematic Review and Meta-analysis. Urology journal 17(2): 109-117	- More recent systematic review included that covers the same topic
Yang, Yue, Chen, Shouzhen, Chen, Fan et al. (2015) Outcome of radiofrequency ablation over	- More recent systematic review included that covers the same topic

Study	Reason
partial nephrectomy for small renal mass (<4 cm): a systematic review and meta-analysis. International journal of clinical and experimental medicine 8(11): 20670-4	
Yin, Xiaotao, Cui, Liang, Li, Fanglong et al. (2015) Radiofrequency Ablation Versus Partial Nephrectomy in Treating Small Renal Tumors: A Systematic Review and Meta-Analysis. Medicine 94(50): e2255	- More recent systematic review included that covers the same topic
Yoo, Sangjun, You, Dalsan, Jeong, In Gab et al. (2017) Preserving Renal Function through Partial Nephrectomy Depends on Tumor Complexity in T1b Renal Tumors. Journal of Korean medical science 32(3): 495-501	- Primary study covered fully by an included systematic review
Yoon, Young Eun, Lee, Hyung Ho, Kim, Ki Hong et al. (2018) Focal therapy versus robot-assisted partial nephrectomy in the management of clinical T1 renal masses: A systematic review and meta-analysis. Medicine 97(45): e13102	- Study does not contain a relevant intervention
Yoshida, Kazuhiko, Oida, Nao, Kondo, Tsunenori et al. (2024) Surgical and functional outcomes of repeat robot-assisted laparoscopic partial nephrectomy compared with repeat open partial nephrectomy. International journal of urology : official journal of the Japanese Urological Association 31(4): 355-361	- Exclude Review C. - Study included only patients T1-T2
You, Dalsan, Jeong, In Gab, Song, Cheryn et al. (2015) Analysis of pre-operative variables for identifying patients who might benefit from upfront cytoreductive nephrectomy for metastatic renal cell carcinoma in the targeted therapy era. Japanese journal of clinical oncology 45(1): 96-102	- Data not reported in an extractable format
Youn, C.S., Park, J.M., Lee, J.Y. et al. (2013) Comparison of laparoscopic ra diofrequency a blation and open partial nephrectomy in patients with a small renal mass. Korean Journal of Urology 54(9): 603-608	- Primary study covered fully by an included systematic review
Yu, Jie, Liang, Ping, Yu, Xiao-ling et al. (2014) US-guided percutaneous microwave ablation versus open radical nephrectomy for small renal cell carcinoma: intermediate-term results. Radiology 270(3): 880-7	- Non-OECD country
Yu, Kun, Liu, Meiping, Xie, Zhenguo et al. (2020) Comparison of efficacy and long-term	- Non-OECD country

Study	Reason
survival of laparoscopic radical nephrectomy with partial nephrectomy in the treatment of patients with early renal cell carcinoma Running title: laparoscopic radical nephrectomy. Journal of B.U.ON. : official journal of the Balkan Union of Oncology 25(2): 1155-1160	
Zaid, Harras B, Parker, William P, Safdar, Nida S et al. (2017) Outcomes Following Complete Surgical Metastasectomy for Patients with Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. The Journal of urology 197(1): 44-49	- Mixed population of SACT pre/post non-pharmacological regimens
Zaorsky, Nicholas G, Lehrer, Eric J, Kothari, Gargi et al. (2019) Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. European urology oncology 2(5): 515-523	- Exclude - wrong population - Study did not compare the interventions of interest
Zargar, Homayoun, Bhayani, Sam, Allaf, Mohamad E et al. (2014) Comparison of perioperative outcomes of robot-assisted partial nephrectomy and open partial nephrectomy in patients with a solitary kidney. Journal of endourology 28(10): 1224-30	- Exclude - For Review C. Proportion of patients stage T3 < 90%
Zeng, Zhiqiang, Ge, Si, Li, Yunxiang et al. (2024) Perioperative and Oncological Outcomes of Partial Versus Radical Nephrectomy for Complex Renal Tumors (RENAL Score >= 7): Systematic Review and Meta-Analysis. Annals of surgical oncology 31(7): 4762-4772	- Systematic review used as source of primary studies
Zhang, Fan, Hu, Jiang-Sheng, Zhang, Kai-Yu et al. (2023) Perioperative, functional, and oncologic outcomes of laparoscopic partial nephrectomy versus open partial nephrectomy for complex renal tumors: a systematic review and meta-analysis. Frontiers in oncology 13: 1283935	- Exclude - For Review C. Proportion of patients stage T3 < 90%
Zhang, M., Zhao, Z., Duan, X. et al. (2018) Partial versus radical nephrectomy for T1b-2N0M0 renal tumors: A propensity score matching study based on the SEER database. PLoS ONE 13(2): e0193530	- SEER database overlap
Zhang, Y., Hu, J., Xie, Y. et al. (2022) Selection of Optimal Candidates for Cytoreductive Nephrectomy in Patients with Metastatic Clear Cell Renal Cell Carcinoma: A Predictive Model	- Mixed population of SACT pre/post non-pharmacological regimens

Study	Reason
Based on SEER Database. Frontiers in Oncology 12: 814512	
Zhang, Yu, Bi, Hai, Yan, Ye et al. (2023) Comparative analysis of surgical and oncologic outcomes of robotic, laparoscopic and open radical nephrectomy with venous thrombectomy: a propensity-matched cohort study. International journal of clinical oncology 28(1): 145-154	- Non-OECD country
Zhang, Yuanyuan, Schoenhals, Jonathan, Christie, Alana et al. (2019) Stereotactic Ablative Radiation Therapy (SAbR) Used to Defer Systemic Therapy in Oligometastatic Renal Cell Cancer. International journal of radiation oncology, biology, physics 105(2): 367-375	- Not a relevant study design - Mixed population of SACT pre/post non-pharmacological regimens
Zhang, Yucong, Long, Gongwei, Shang, Haojie et al. (2021) Comparison of the oncological, perioperative and functional outcomes of partial nephrectomy versus radical nephrectomy for clinical T1b renal cell carcinoma: A systematic review and meta-analysis of retrospective studies. Asian journal of urology 8(1): 117-125	- Systematic review used as source of primary studies
Zhang, Zhao, Wu, Hongliang, Yang, Tong et al. (2020) Metastatic renal cell carcinoma patients of T4 stage who are in status of N1 stage or older than 76 years cannot benefit from cytoreductive nephrectomy. BMC cancer 20(1): 844	- Mixed population of SACT pre/post non-pharmacological regimens *No information regarding SACT in both arms*
Zhao, Kaidong, Kim, Eric H, Vetter, Joel M et al. (2020) Laparoscopic cytoreductive nephrectomy is associated with significantly improved survival compared with open cytoreductive nephrectomy or targeted therapy alone. Molecular and clinical oncology 13(6): 71	- Exclude - Outcome was measured using a measure out of scope *OS reported in median months*
Zhao, Z., Wu, W., Duan, X. et al. (2019) The value of cytoreductive nephrectomy on the survival of metastatic renal carcinoma patients based on the number of site-specific metastases. PLoS ONE 14(4): e0215861	- Mixed population of SACT pre/post non-pharmacological regimens *No information about the treatment received by non CN arm reported. The sequence of SACT reported is also not reported.*
Zhou, Minerva, Mills, Abigail, Noda, Christopher et al. (2018) SEER study of ablation versus partial nephrectomy in cT1A renal cell carcinoma. Future oncology (London, England) 14(17): 1711-1719	- Secondary publication of an included study that does not provide any additional relevant information *SEER database - more fully covered in another included study*

Study	Reason
Zhuang, W, Chen, J, Li, Y et al. (2019) The effect of cytoreductive partial nephrectomy in elderly patients with metastatic renal cell carcinoma：a systematic review. ResearchSquare	- Exclude - Outcome was measured using a measure out of scope
Zini, Laurent, Perrotte, Paul, Jeldres, Claudio et al. (2008) Nephrectomy improves the survival of patients with locally advanced renal cell carcinoma. BJU international 102(11): 1610-4	- Comparator in study does not match that specified in protocol *Nephrectomy vs no surgery*

Economic studies

HE excluded at full text (n=2)

Study	Reason for exclusion
Health Improvement Scotland (2011) Evidence Note: Is radiofrequency ablation treatment a clinically and cost effective treatment to be offered to people with renal cancer in NHS Scotland? Is radiofrequency ablation treatment a clinically and cost effective treatment to be offered to people with renal cancer in NHSScotland? (york.ac.uk)	-Based on a US health economics study with a quasi-societal perspective and US costs.
Iossa, Vincenzo, Pandolfo, Savio Domenico, Buonopane, Roberto et al. (2025) Robot-assisted partial nephrectomy vs. percutaneous cryoablation for T1a renal tumors: a single-center retrospective analysis of outcomes and costs. International urology and nephrology 57(4): 1097-1104	- Exclude - cost analysis only, did not have a QoL outcome

Appendix K– Research recommendations – full details

K1.1 Research recommendation 1

What is the clinical and cost effectiveness of metastasectomy before systemic anticancer therapy (SACT) or after SACT has been started compared with SACT alone for people with metastatic renal cell carcinoma who have had their primary mass removed?

K1.1.1 Why this is important

Metastasectomy is an option to treat metastases from RCC, particularly after the person has had a good response to systemic anti-cancer therapy (SACT). However, there is a lack of data about its effectiveness.

K1.1.2 Rationale for research recommendation 1

Table 15: Rationale for research recommendation 1

Importance to 'patients' or the population	Metastasectomy could be used to remove metastases after a good response to SACT, which could mean the person has no visible evidence of disease on imaging. This would be a meaningful milestone for many people
Relevance to NICE guidance	Metastasectomy has been considered in this guideline and there is a lack of data on effectiveness before or after SACT
Relevance to the NHS	The outcome would affect the types of non-pharmacological interventions for metastatic RCC provided by the NHS
National priorities	Low
Current evidence base	No evidence was identified about metastasectomy specifically before or after SACT
Equality considerations	None known

K1.1.3 Modified PICO table

Table 16: Modified PICO table

Population	Adults (18 years or over) with metastatic RCC who have had their primary lesion treated and who have only metastatic disease remaining
Intervention	• Metastasectomy before SACT or • Metastasectomy after SACT has been started
Comparator	Interventions compared with each other or with SACT alone
Outcome	Progression-free survival Overall survival Cancer-specific survival Adverse events Quality of life Duration of hospital stay Cost effectiveness

Study design	Randomised controlled trials Comparative cohort studies
Timeframe	All
Additional information	Studies must present results separately for before and after SACT

K1.2 Research recommendation 2

What is the clinical and cost effectiveness of thermal ablation after systemic anticancer therapy (SACT) has been started compared to SACT alone for treating metastases in people with metastatic renal cell carcinoma?

K1.1.1 Why this is important

Thermal ablation is an option to treat metastases from RCC under certain circumstances. However, there is a lack of data about its effectiveness after SACT has been started compared to SACT alone. (SABR is not included in this research recommendation because there are ongoing clinical trials looking at this.)

K1.1.2 Rationale for research recommendation 2

Table 17: Rationale for research recommendation 2

Importance to 'patients' or the population	For people who are healthy enough to receive additional intervention once they have started SACT for metastases from RCC, thermal ablation of metastases could further control and reduce disease.
Relevance to NICE guidance	Thermal ablation has been considered in this guideline and there is a lack of data on effectiveness after SACT has been started.
Relevance to the NHS	The outcome would affect the types of non-pharmacological interventions for metastatic RCC provided by the NHS.
National priorities	Low
Current evidence base	No evidence was identified about these interventions after SACT has been started.
Equality considerations	None known

K1.1.3 Modified PICO table

Table 18: Modified PICO table

Population	Adults (18 years or over) with metastatic RCC
Intervention	Thermal ablation after SACT has been started
Comparator	SACT alone
Outcome	Progression-free survival Overall survival Cancer-specific survival Adverse events Quality of life

	Duration of hospital stay Cost effectiveness
Study design	Randomised controlled trials Comparative cohort studies
Timeframe	All
Additional information	None

K1.3 Research recommendation 3

What is the clinical and cost effectiveness of stereotactic ablative radiotherapy for treating the primary mass after systemic anticancer therapy has been started in people with locally advanced inoperable renal cell carcinoma?

K1.3.1 Why this is important?

Stereotactic ablative radiotherapy (SABR) has a potential role in locally advanced inoperable disease after SACT if there has been sufficient downstaging of the primary tumour to facilitate radiotherapy.

K1.3.2 Rationale for research recommendation 3

Table 19: Rationale for research recommendation

Importance to 'patients' or the population	For people who are healthy enough to receive additional intervention once they have started SACT for locally advanced inoperable disease, SABR could further control and reduce disease after there has been downstaging of the tumour.
Relevance to NICE guidance	SABR have been considered in this guideline and there is a lack of data on effectiveness after SACT has been started.
Relevance to the NHS	The outcome would affect the types of non-pharmacological interventions for locally advanced inoperable RCC provided by the NHS.
National priorities	Low
Current evidence base	No evidence was identified for the use of SABR in locally advanced inoperable disease after SACT.
Equality considerations	None known

K1.3.3 Modified PICO table

Table 20: Modified PICO table

Population	Adults (18 years or over) with locally advanced inoperable RCC
Intervention	SABR after SACT has been started
Comparator	SACT alone
Outcome	Progression-free survival Overall survival Cancer-specific survival Adverse events

	Quality of life Duration of hospital stay Cost effectiveness
Study design	Randomised controlled trials Comparative cohort studies
Timeframe	All
Additional information	None