Bijlagen bij richtlijnmodules Niercelcarcinoom

Inhoudsopgave

Bijlagen bij module 1

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Overweeg bij cT1b niertumoren nefronsparende behandeling.	1-3 jaar	Niet bekend, maar naar inschatting neutraal	bekendmaking richtlijn	Gebrek aan kennis over module	bekendmaken richtlijn	NVU, NVRO	
Bepaal het behandeladvies in een multidisciplinair overleg en registreer de conclusie en overwegingen. Gebruik RENAL nephrometry score bij bepalen van de behandelstrategie en registreer deze in het radiologie verslag en de conclusie van het	1-3 jaar	Niet bekend maar naar inschatting neutraal	bekendmaking richtlijn	-	bekendmaken richtlijn	NVU, NVRO	

multidisciplinair overleg.							

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Research question: What are the (un)favorable effects of partial nephrectomy, total nephrectomy, SABR, percutaneous ablation in patients with non-metastatic renal cell carcinoma between 4-7 cm?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Jiang, 2019 PICO1a [individual study characteristics deduced from [Jiang, 2019]]	SR and meta-analysis of retrospective cohort studies *Literature search up to March 2018* **A**: Kim, 2012 **B**: Badalato, 2011 **C**: Jang, 2016 **D**: Iizuka, 2012 **E**: Roos, 2011 **F**: Roos, 2012	Inclusion criteria SR: - comparative partial nephrectomy or nephron-sparing surgery and radical nephrectomy for the treatment of 4-7 cm renal tumors - evaluation of at least one	Describe intervention: **A**: partial nephrectomy **B**: partial nephrectomy **C**: partial nephrectomy **D**: partial nephrectomy **E**: partial nephrectomy **F**: partial nephrectomy **G**: partial nephrectomy **H**: partial nephrectomy **I**: partial nephrectomy **J**: partial nephrectomy **K**: partial nephrectomy **L**: partial nephrectomy	Describe control: **A**: radical nephrectomy **B**: radical nephrectomy **C**: radical nephrectomy **D**: radical nephrectomy **E**: radical nephrectomy **F**: radical nephrectomy **G**: radical nephrectomy **H**: radical nephrectomy **I**: radical nephrectomy **J**: radical nephrectomy **K**: radical nephrectomy **L**: radical nephrectomy	End-point of follow-up **A**: 78.2 vs 66.5 months **B**: 120 months **C**: 48.1 vs 42.6 months **D**: 31.3 vs 93.0 months **E**: 55.2 vs 78 months **F**: 120 months **G**: 40.7 vs 46.7 months **H**: 168 months **I**: 57.6 months **J**: 39.5 vs 46.9 months **K**: 120 months **L**: 60 vs 120 months	Outcome measure-1: 5-year and 10-year overall survival *5-year overall survival* Effect measure: RR (95% CI): **A**: 1.07 (0.92 to 1.24) **B**: 0.97 (0.94 to 1.00) **C**: 1.14 (1.07 to 1.22) **D**: 1.15 (1.08 to 1.22) **E**: 0.97 (0.85 to 1.11) **F**: 0.98 (0.87 to 1.10) **H**: 1.16 (0.97 to 1.37) **N**: 1.03 (0.81 to 1.31)	Brief description of author's conclusion - PN may provide comparable outcomes in terms of recurrence-free survival and overall survival, and better renal function preservation. - RN ensures a better cancer-special survival compared to PN. - PN had an equal incident of postoperative complications compared to RN.

PS., study characteristics and results are extracted from the SR (unless stated otherwise)	**G**: Crepel, 2010 **H**: Milonas, 2013 **I**: Thompson, 2009 **J**: Pignot, 2014 **K**: Antonelli, 2012 **L**: Meskawi, 2013 **M**: Weight, 2010 **N**: Simmons, 2009 **O**: Robert, 2006 **P**: Patard, 2004 <u>Study design</u>: Retrospective cohort <u>Setting and Country</u>: Not mentioned <u>Source of funding and conflicts of interest:</u> Not mentioned for individual studies	oncological result such as recurrence-free survival, cancer-special survival, and overall survival <u>Exclusion criteria SR:</u> - case reports, reviews, and articles without applicable data - studies that included both T1b and T2 or renal tumors larger than 7 cm - studies that were not comparative in nature *16 studies included* <u>Important patient characteristics at baseline</u>: *N, mean age* **A**: 18 patients, 47.3 yrs vs 52 patients, 57.3 yrs **B**: 1047 patients, 58.4 yrs vs 10,209 patients, 60.7 yrs **C**: 100 patients, 55.3 yrs vs 100 patients, 55.7 yrs	**M**: partial nephrectomy **N**: partial nephrectomy **O**: partial nephrectomy **P**: partial nephrectomy	**M**: radical nephrectomy **N**: radical nephrectomy **O**: radical nephrectomy **P**: radical nephrectomy	**M:** 49 vs 41 months **N:** NA **O:** 34.0 vs 48.5 months **P:** 120 months <u>For how many participants were no complete outcome data available?</u> Not reported	Pooled effect (fixed effects model): 1.02 [95% CI 1.00 to 1.05] favoring radical nephrectomy Heterogeneity (I^2): 84% *10-year overall survival* Effect measure: RR (95% CI): **C:** 1.18 (1.02 to 1.36) **D:** 1.48 (1.34 to 1.64) **E:** 0.98 (0.84 to 1.16) **F:** 0.85 (0.71 to 1.00) **G:** 1.61 (1.48 to 1.74) **H:** 1.04 (0.76 to 1.43) Pooled effect (random effects model): 1.17 [95% CI 0.95 to 1.44] favoring radical nephrectomy Heterogeneity (I^2): 93% <u>Outcome measure-2: 5-year and 10-year cancer-special survival</u> *5-year overall cancer-special survival* Effect measure: RR (95% CI): **A**: 1.00 (0.88 to 1.14) **E**: 0.97 (0.91 to 1.04) **F**: 0.98 (0.87 to 1.10) **H**: 1.20 (1.11 to 1.30) **K**: 0.97 (0.92 to 1.02) **L**: 1.02 (1.01 to 1.03) **M**: 1.04 (1.01 to 1.07) **N**: 1.07 (0.84 to 1.38) **O**: 0.98 (0.92 to 1.05) Pooled effect (fixed effects model): 1.02 [95% CI 1.01 to 1.03] favoring radical nephrectomy Heterogeneity (I^2): 68%	<u>Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question</u> - Only included non-RCTs - LnRR was used instead of LnHR for overall survival, cancer-special survival, and recurrence-free survival - Wrong study included in forest plot for declined eGFR - High levels of heterogeneity because of bias <u>Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading</u> Jiang 2019 used the GRADE approach for evidence grading. For all the outcomes, a moderate quality of evidence was found but no explanation was provided. <u>Sensitivity analyses:</u> Jiang 2019 sequentially omitted a single study one by one to determine which studies contributed the most to the heterogeneity of the results. <u>Heterogeneity: clinical and statistical heterogeneity; explained versus unexplained (subgroup analysis)</u>

		D: 67 patients, 57.6 yrs vs 195 patients, 58.1 yrs **E:** 73 patients, 60.4 yrs, 100 patients, 61.1 yrs **F**: 85 patients vs 118 patients (age unknown) **G**: 275 patients, 60.5 yrs vs 1100 patients, 60.5 yrs **H:** 34 patients, 62.2 yrs vs 317 patients, 63.4 yrs **I:** 286 patients vs 873 patients (age unknown) **J:** 123 patients, 57.6 yrs vs 185 patients, 61.6 yrs **K:** 198 patients, 58.2 yrs vs 1426 patients, 62.4 yrs **L:** 1526 patients, 60.3 yrs vs 6104 patients, 60.6 yrs **M**: 212 patients, 49 yrs vs 298 patients, 41 yrs **N:** 35 patients, 63.5 yrs vs 75 patients, 63.4 yrs **O**: 33 patients, 68.9 yrs vs 66 patients, 66.9 yrs **P:** 64 patients vs 576 patients (age unknown) *Sex:*				*10-year overall cancer-special survival* Effect measure: RR (95% CI): **C:** 1.02 (0.93 to 1.11) **E**: 0.95 (0.87 to 1.04) **F**: 0.95 (0.88 to 1.03) **H**: 1.04 (0.87 to 1.25) **I**: 1.12 (1.04 to 1.20) **K**: 1.03 (0.98 to 1.09) **L**: 1.05 (1.03 to 1.06) Pooled effect (fixed effects model): 1.04 [95% CI 1.03 to 1.06] favoring radical nephrectomy Heterogeneity (I^2): 57% <u>Outcome measure-3: 5-year and 10-year recurrence-free survival</u> *5-year recurrence-free survival* Effect measure: RR (95% CI): **A**: 1.23 (1.02 to 1.48) **C**: 1.00 (0.89 to 1.12) **E**: 0.92 (0.82 to 1.03) **F**: 0.98 (0.94 to 1.03) **K**: 0.99 (0.98 to 1.01) **N**: 0.97 (0.89 to 1.06) Pooled effect (fixed effects model): 0.99 [95% CI 0.98 to 1.01] favoring partial nephrectomy Heterogeneity (I^2): 31% *10-year recurrence-free survival* Effect measure: RR (95% CI): **C:** 1.21 (1.02 to 1.44) **E:** 0.92 (0.82 to 1.03)	The selection bias present in the included studies with regards to the tumor pathology (clear-cell carcinoma vs non-clear cell carcinoma) may account for the higher heterogeneity of the 10-year overall survival outcome. After sensitivity analysis and meta-regression, no explicit causes of heterogeneity have been detected.

		A: 72.2% male vs 69.2% male **B**: 35.4% male vs 59.2% male **C**: 71% male in both groups **D:** 76.1% male vs 61.0% male **E**: 90.4% male vs 38% male **F**: 65.9% male vs 73.7% male **G**: 63.6% male vs 60.6% male **H**: 44.1% male vs 51.7% male **I:** 68.5% male vs 61.6% male **J**: 65.0% male vs 68.7% male **K**: 67.7% male vs 63.3% male **L:** 67.7% male vs 67.8% male **M**: 65.6% male vs 59.1% male **N**: 74.3% male vs 52.0% male **O**: 78.8% male vs 66.7% male **P**: NA *Pathologic tumor size (cm):* **A**: 5.0 vs 5.5 **B**: 4.86 vs 5.27 **C**: 4.9 vs 4.9 **D**: 4.9 vs 5.3 **E:** 5.0 vs 5.5 **F:** NA **G**: NA **H**: 4.67 vs 5.25				Pooled effect (fixed effects model): 1.00 [95% CI 0.91 to 1.10] (no effect) Heterogeneity (I^2): 85% <u>Outcome measure-4: post-operative complications</u> Effect measure: OR (95% CI): **C**: 1.43 (0.62 to 3.28) **E**: 1.47 (0.87 to 2.50) **H**: 1.36 (0.38 to 4.83) Pooled effect (fixed effects model): 1.45 [95% CI 0.95 to 2.21] favoring radical nephrectomy Heterogeneity (I^2): 0% <u>Outcome measure-5: declined eGFR</u> Effect measure: mean difference (95% CI): **A**: -6.10 (-11.51 to -0.69) **J**: -4.70 (-8.15 to -1.25) **M**: -15.00 (-17.29 to -12.71) Pooled effect (fixed effects model): -11.21 [95% CI -13.01 to -9.41] favoring partial nephrectomy Heterogeneity (I^2): 93%	

		I: NA **J**: 5.2 vs 5.5 **K**: 5.0 vs 5.7 **L**: 5.14 vs 5.15 **M**: 4.8 vs 5.6 **N**: 4.6 vs 5.3 **O**: 5.2 vs 5.2 **P**: 5.3 vs 5.6 Unknown if groups were comparable at baseline					
Chan, 2022 PICO 1b [individual study characteristics deduced from [Chang, 2022]] PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of retrospective cohort studies *Literature search up to June 2020* Only studies about T1b described **A**: Andrews, 2019 **B**: Caputo, 2017 **C**: Shapiro, 2019 **D**: Rembeyo 2020 **E**: Liu, 2017 **F**: Pecoraro, 2019 **G**: Yanagisawa, 2018 **H**: Chang, 2015 <u>Study design</u>: Retrospective cohort <u>Setting and Country</u>: **A**: USA	<u>Inclusion criteria SR:</u> - Studies comparing the use of ablative therapies and partial nephrectomy in patients with T1a or T1b small renal masses - All randomized controlled trials or observational studies - Only studies reporting the outcome of interest including survival outcomes and peri-operative outcomes <u>Exclusion criteria SR:</u> - Studies solely focusing on	<u>Describe intervention</u>: **A**: Percutaneous cryoablation **B**: Laparoscopic or percutaneous cryoablation **C**: Percutaneous microwave partial nephrectomy **D**: Percutaneous cryoablation or radiofrequency ablation **E**: Percutaneous radiofrequency ablation **F**: Cryoablation **G**: Percutaneous cryoablation **H**: Radiofrequency ablation	<u>Describe control:</u> **A**: Partial nephrectomy **B**: Robot-assisted partial nephrectomy **C**: Non-specified partial nephrectomy **D**: Robot-assisted partial nephrectomy **E**: Open or laparoscopic partial nephrectomy **F**: Partial nephrectomy **G**: Partial nephrectomy **H**: Partial nephrectomy	<u>End-point of follow-up</u> **A**: Median [IQR] PN: 8.7 [6.9-11.3] years CYRO: 6.0 [4.0-7.2] years **B**: Median [IQR] PN: 13.0 [3.19-19.2] months CYRO: 30.1 [13.2-64.0] months **C**: Median [IQR] MW: 33.9 [21.7-61.2] months PN: 35.1 [9.5-89] months **D**: Median [Range] CA: 19.9 (15.5-27.2) months RFA: 51.3 (31.1-56.5) months PN: 23.7 (15.5-32.2) months **E**: Median [Range] Full cohort: 78 [8-132] months **F**: Median: 38 months **G**: Median CRYO: 22 months PN: 17 months **H**: Mean [SD] RFA: 65.9 [17.9] PN: 70.2 [11.7]	<u>Outcome measure-1: Overall complications</u> <u>Rates of overall complications in T1b patients by approach</u> *Percutaneous* Effect measure: RR (95% CI): **C**: 0.72 (0.33 to 1.58) **D**: 1.40 (0.65 to 3.04) **E**: 1.30 (0.47 to 3.59) **G**: 0.77 (0.21 to 2.82) *Not Specified/Mixed* **B**: 0.54 (0.25 to 1.17) **H**: 2.51 (0.72 to 8.72) Pooled effect (random effects model): 0.97 [95% CI 0.63 to 1.50] favoring ablation Heterogeneity (I^2): 22.33% <u>Rates of overall complications in T1b patients by energy source</u> *Cryoablation*	<u>Brief description of author's conclusion</u> AT have similar long-term oncological durability; lower rates of complications and superior kidney function preservation compared to PN. Given the low quality of evidence, AT is a reasonable alternative to PN in frail and co-morbid patients. Long-term high-quality studies are needed to confirm the potential benefits of AT, especially in T1b patients. <u>Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question</u> - Study of Chang 2015 included in forest plot, but not explained in characteristics table - High risk of bias and low confidence, especially confounding and selection

	B: USA **C**: USA **D**: France **E**: China **F**: Canada **G**: Japan **H**: China <u>Source of funding and conflicts of interest:</u> **A**: None declared **B**: 1 author received consultancy fees from a relevant company **C**: 5 authors are consultants, 1 author received prior grant funding. No external funding **D**: None declared **E**: Funding received from National Natural Science Foundation of China **F**: None declared **G**: Not reported **H**: Not reported	solitary kidneys, bilateral tumors, or patients with inherited RCC syndromes - Studies focusing on T1 solely without stratifying results into T1a and T1b - Letters, editorials, single-arm studies, pediatric studies, and non-human studies *8 studies included* <u>Important patient characteristics at baseline</u>: *Average age (years)* **A**: Median [IQR] PN: 61 [52-70] CYRO: 77 [69.5-83] **B:** Median [IQR] *Unmatched:* CYRO: 68 (64-76) PN: 61 (52-68) *Matched*: CYRO: 68 (64-76) PN: 68 (64-76) **C**: Median [IQR] MWA: 69 [65-77] PN: 58 [51-65] **D**: Median [Range] CYRO: 72 [60.0-80.0]			<u>For how many participants were no complete outcome data available?</u> Not reported	**B:** 0.54 (0.25 to 1.17) **G**: 0.77 (0.21 to 2.82) *RFA* **E**: 1.30 (0.47 to 3.59) **H**: 2.51 (0.72 to 8.72) *MWA* **C**: 0.72 (0.33 to 1.58) *Not Specified/Mixed* **D**: 1.40 (0.65 to 3.04) Pooled effect (random effects model): 0.97 [95% CI 0.63 to 1.50] favoring ablation Heterogeneity (I^2): 22.33% <u>Outcome measure-2: Minor complications</u> <u>Rates of minor complications in T1b patients by approach</u> *Not specified or mixed* **B:** 0.67 (0.27 to 1.65) **H:** 4.30 (0.51 to 36.07) *Percutaneous* **C:** 0.40 (0.12 to 1.30) **D:** 1.40 (0.65 to 3.04) **E:** 1.11 (0.38 to 3.21) Pooled effect (random effects model): 0.96 [95% CI 0.57 to 1.61] favoring ablation Heterogeneity (I^2): 16.67% <u>Rates of minor complications in T1b patients by energy source</u>	bias of included patients. Tend to favor the control group <u>Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading</u> Certainty of evidence was assessed with GRADE. A very low GRADE was found for all outcomes: - Cancer-specific survival - Overall survival - Metastatic-Free survival - Disease-Free survival - Overall post-operative complications - Minor post-operative complications - Major post-operative complications - Change in renal function post-operatively <u>Sensitivity analyses:</u> Planned sensitivity analyses were performed based on the RoB assessment, using studies with propensity-matched analyses or with a minimum follow-up time of 5-years. Sensitivity analyses were also performed on large population-based studies which may have a dominating effect on the outcome. <u>Heterogeneity: clinical and statistical heterogeneity; explained versus</u>

		RFA: 84 [76.0-86.0] PN: 60 [54.8-66.0] **E:** Median [Range] *Clear-cell (cc) RCC* PRFA: 68 [35-85] PN: 58.5 [23-83] *Non clear-cell (ncc) RCC* PRFA: 65.5 [33-84] PN: 55 [24-84] **F**: Median CYRO: 71 PN: 61 **G**: NR (Patients in the CYRO group had significantly higher age) **H:** Mean [SD] RFA: 64.0 [8.4] PN: 56.9 [9.9] *Average tumour size (cm)* **A**: Median [IQR] PN: 5.0 [4.5-5.5] CYRO: 4.8 [4.4-5.6] **B**: Median [IQR] *Unmatched* CYRO: 4.3 [4.2-4.7] PN: 5.0 [4.5-5.6] *Matched* CYRO: 4.3 (4.2-4.7) PN: 4.6 (4.3-4.9) **C:** Median [IQR] MWA: 4.4 [4.1-5] PN: 4.7 [4.1-5.3]				*Cryoablation* **B**: 0.67 (0.27 to 1.65) *RFA* **E**: 1.11 (0.38 to 3.21) **H**: 4.30 (0.51 to 36.07) *MWA* **C**: 0.40 (0.12 to 1.30) *Not specified or mixed* **D**: 1.40 (0.65 to 3.04) Pooled effect (random effects model): 0.96 [95% CI 0.57 to 1.61] favoring ablation Heterogeneity (I^2): 16.67% <u>Outcome measure-3: Rates of major complications in T1b patients by approach</u> *Not specified or mixed* **B**: 0.25 (0.03 to 2.11) **H**: 1.61 (0.29 to 8.91) *Percutaneous* **C:** 0.53 (0.19 to 1.50) **D:** Not estimated **E:** 3.70 (0.15 to 89.94) **G**: 0.77 (0.07 to 8.07) Pooled effect (random effects model): 0.69 [95% CI 0.33 to 1.47] favoring ablation Heterogeneity (I^2): 0% <u>Rates of major complications in T1b patients by energy source</u> *Cryoablation*	<u>unexplained (subgroup analysis)</u> Planned subgroup analyses of different energy sources and approaches of AT were performed to identify potential sources of heterogeneity to inform clinical practice

		D: Median [Range] CYRO: 4.6 (4.1-5.4) RFA: 4.2 (4.0-4.5) PN: 4.5 (4.0-5.45) **E:** Median [Range] *ccRCC* PRFA: 5.5 [4.3-7] PN: 5.8 [4.2-7] *nccRCC* PRFA: 5.5 [4.4-7] PN: 5.5 [4.2-7] **F**: Median CYRO: 4.69 PN: 5.10 **G**: Mean CYRO: 4.55 PN: 4.59 **H:** Mean [SD] RFA: 4.7 [0.5] PN: 5.2 [0.6] Groups were not comparable at baseline.				**B**: 0.25 (0.03 to 2.11) **G**: 0.77 (0.07 to 8.07) *RFA* **E:** 3.70 (0.15 to 89.94) **H:** 1.61 (0.29 to 8.91) *MWA* **C**: 0.53 (0.19 to 1.50) *Not specified or mixed* **D**: Not estimated Pooled effect (random effects model): 0.69 [95% CI 0.33 to 1.47] favoring ablation Heterogeneity (I^2): 0% <u>Outcome measure-4: Oncological outcomes</u> These single-centre studies display contradicting results, and it is important to note the potential for operator bias, leading to significant difference in oncological outcomes <u>Outcome measure-5: Change in eGFR post-operatively</u> In T1b disease, four studies investigated change in eGFR pre- and post-operatively: two found the change to be similar while two found mixed approaches of RFA to have a significantly smaller drop in eGFR compared to PN	

Evidence table for intervention studies

Research question: What are the (un)favorable effects of partial nephrectomy, total nephrectomy, SABR, percutaneous ablation in patients with non-metastatic renal cell carcinoma between 4-7 cm?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Chong, 2018	Type of study: Retrospective cohort study Setting and country: The American College of Surgeons' National Cancer Database (NCDB) was applied from 2004 to 2013 Funding and conflicts of interest: This research received no specific grant from any funding agency in the public, commercial, or not-for-	Inclusion criteria: Patients with renal cancer who underwent partial nephrectomy or radical nephrectomy as definitive treatment from 2004 to 2013 Exclusion criteria: - Patients with clinical T2-4, N1, or M1 renal cell carcinoma - Patients with missing clinical stage data - Patients with renal tumors	Describe control (treatment/procedure/test): Radical nephrectomy (RN)	Describe intervention (treatment/procedure/test): Partial nephrectomy (PN)	Length of follow-up: Median follow up was 44.5 months (IQR 25.7 to 68.1 months) Loss-to-follow-up: Not reported. Incomplete outcome data: A complete case analysis was conducted and patients with missing data on baseline characteristics, survival, or readmission were excluded.	Outcome measures and effect size (include 95%CI and p-value if available): Overall survival *Unadjusted analysis:* PN was associated with a lower hazard of death (HR=0.77, 95% CI 0.69 to 0.86, p<0.001). *IPTW-adjusted Cox proportional hazards regression:* PN associated with improved overall survival (HR = 0.89, 95% CI 0.82 to 0.99, p=0.025) *Sandwich-type variance estimator:* HR = 0.89, 95% CI 0.79 to 1.02, p =0.106 *5-year IPTW-KM:*	Author's conclusion PN compared with RN was associated with a modest survival benefit for patients with a cT1b renal mass. PN should be offered over RN when feasible despite a marginal increase in unplanned hospital readmissions for PN of cT1b tumors. Remarks: Sensitivity analyses for pre-2012 and adjusting for all covariates

	profit sectors. No conflicts of interest were reported.	excised bilaterally or a horseshoe kidney - Patients receiving additional treatments - Patients with concurrent or prior cancer diagnosis N total at baseline: Intervention: 12,656 Control: 4419 Important prognostic factors[2]: *Age ± SD:* *I: 62.1 (11.3)* *C: 60.7 (10.6)* *p <0.001* *Sex:* *I: 59.2% M* *C: 65.8% M* *p <0.001* Groups not comparable at baseline				85.3% for PN 84.3% for RN *10-year IPTW-KM:* 70.8% for PN 63.6% for RN	
Venkatramani, 2018	Type of study:	Inclusion criteria:	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	Length of follow-up:	Outcome measures and effect size	Author's conclusion

	Retrospective cohort study <u>Setting and country</u>: National Cancer Data Base (NCDB) from US between 2004 and 2013 <u>Funding and conflicts of interest</u>: Not reported.	- Patients diagnosed with renal cell carcinoma - Clinical stage cT1b-T2N0M0 <u>Exclusion criteria</u>: - Patients diagnosed at death or autopsy - Missing or unknown data for clinical TNM stage <u>N total at baseline</u>: *1:1 propensity score matching (for T1b)* Intervention: 5,534 Control: 5,534 <u>Important prognostic factors</u>[2]: Not specified for T1b patients <u>Unknown if groups were</u>	Partial nephrectomy (PN)	Radical nephrectomy (RN)	Median follow-up was 35.6 months for PN and 45.1 months for RN <u>Loss-to-follow-up</u>: Not reported. <u>Incomplete outcome data</u>: No missing data.	(include 95%CI and p-value if available): <u>Overall survival</u> Multivariate Cox proportional hazard model: HR = 0.81 (0.73 to 0.90) favouring partial nephrectomy (p<0.001)	PN was associated with a significantly better overall survival than RN for cT1b. <u>Remarks:</u> Numbers in text and tables do not match

		comparable at baseline					

Table of quality assessment for systematic reviews of RCTs and observational studies

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Jiang, 2019 PICO 1a	No. Only a study aim was mentioned and inclusion criteria not much specified.	Yes. Search period and search terms described and searched in PubMed, Embase and Cochrane Central Register.	No. Exclusion reason are mentioned but not specified for each individual study.	Yes. Age, sex, and pathologic tumor size were described per individual article.	No. Only individual studies did a multivariate analysis or propensity score matching to eliminate any potential confounding factors.	Yes. Newcastle-Ottowa Scale for risk of bias assessment and GRADE for determining the quality of the evidence.	Unclear. Statistical heterogeneity is assessed (and was high for most outcomes) but clinical heterogeneity is not assessed.	Yes. Funnel plots were made.	No. Conflicts of interest not reported for individual studies.
Chan, 2022 PICO 1b	Yes. PICO described in PROSPERO registration and inclusion criteria were mentioned.	Yes. Search period and search strategy were described. Medline and Embase were searched.	Yes. A list of excluded studies was provided with reasons for exclusion per individual study.	Yes. Baseline characteristics were described for each individual study.	No. No multivariate analysis was performed.	Yes. Risks of biases of observational studies were assessed using the ROBINS-I tool.	Unclear. Statistical heterogeneity is assessed and subgroup analyses to identify potential sources of heterogeneity to inform clinical practice, but clinical heterogeneity is not assessed.	Yes. Funnel plots were made, and Egger's test was performed.	Yes. Conflict of interest reported for systematic review and individual studies.

Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Risk of bias table for interventions studies (cohort studies based on risk of bias tool by the CLARITY Group at McMaster University)

Author, year	Selection of participants Was selection of exposed and non-exposed cohorts drawn from the same population?	Exposure Can we be confident in the assessment of exposure?	Outcome of interest Can we be confident that the outcome of interest was not present at start of study?	Confounding-assessment Can we be confident in the assessment of confounding factors?	Confounding-analysis Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?	Assessment of outcome Can we be confident in the assessment of outcome?	Follow up Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?	Co-interventions Were co-interventions similar between groups?	Overall Risk of bias
Chong, 2018	*Probably yes* Reason: Participants were selected from a registry	*Probably yes* Reason: Received treatment derived from registry data	*Probably yes* Reason: Outcome of interest is overall survival which was derived from registry data	*Probably yes* Reason: Demographic data presented for subgroup of T1b renal tumors	*Definitely yes* Reason: IPTW (inverse probability of treatment weighting) was employed to account for selection bias and confounding by	*Probably yes* Reason: Outcome data derived from registry data and no missing data	*Probably yes* Reason: Follow-up for overall survival seems accurate and outcome data was complete	*No information* Reason: No data available on other interventions besides partial or radial nephrectomy	**Low**

					demographic and clinical covariates				
Venkatramani, 2018	*Probably yes* Reason: Participants were selected from a registry	*Probably yes* Reason: Received treatment derived from registry data	*Probably yes* Reason: Outcome of interest is overall survival which was derived from registry data	*Probably no* Reason: Demographic and pathological characteristics described, but not separately for T1b	*Definitely yes* Reason: Authors performed a 1:1 propensity score matching	*Probably yes* Reason: Outcome data derived from registry data and no missing data	*Probably yes* Reason: Follow-up for overall survival seems accurate and outcome data was complete	*No information* Reason: No data available on other interventions besides partial or radial nephrectomy	**Some concerns**

Table of excluded studies

Reference	Reason for exclusion
Deng, 2020	Robot-assisted partial nephrectomy vs. laparoscopic partial nephrectomy
Mari, 2021	Open partial nephrectomy vs. laparoscopic PN vs. robot-assisted PN. Stage=t1a, t1b en t2
Propiglia, 2016	Open partial nephrectomy vs. laparoscopic PN vs. robot-assisted PN
El-Ghazaly, 2014	SR with 32 case series about partial neprhectomy. No comparison
Bedke, 2008	Reevaluation of the optimal tumor size cutoff point
Bessede, 2015	Nephron-sparing surgery, no comparison.
Best, 2017	Survey study about current opinions
Eggener, 2015	PN with cold ischemia vs. PN with warm ischemia
Ehsanullah, 2021	PN supra 12th rib miniflank incision with zero ischemia, no comparison.
Gill, 2007	Wrong population. Laparoscopic partial nephrectomy vs. open partial nephrectomy.
Gontero, 2021	PN with short life expectancy vs. PN with long life expectancy. Wrong study design.
Kumar, 2017	Videoabstract
Lane, 2015	Potential candidates for PN, no comparison.
Paulucci, 2018	Transperitoneal vs. retroperitoneal robotic partial nephrectomy.
Ponsky, 2015	No comparison, dose-escalation study.
Reynolds, 2017	ct1a vs. ct1b with robotic partial nephrectomy
Salah, 2020	Prediciting outcome of PN with nephrometry score
Schiavina, 2015	Wrong study design. Patients undergoing NSS, with results compared among different periods.
Serni, 2015	Patients treated with simple enucleation, no comparison.
Simone, 2016	Trends in the use of PN (European centers).
Zargar, 2016	Partial nephrectomy, no comparison.
Ljungberg, 2021	Wrong publication type Narrative.
Van Poppel, 2011	Narrative review
Van Poppel, 2013	Narrative review
Weight, 2013	Wrong publication type Narrative.
Furukawa, 2020	Robot-assisted partial nephrectomy, no comparison. T1a vs. t1b.
Mehrazin, 2014	Active surveillance vs. delayed surgical intervention, wrong comparison. Stage=t1b-t2, no separate analyses.
Schachter, 2007	Wrong outcome (histology). Tumor sizes not separate in analyses (stage not mentioned).
Takagi, 2015	PN with renorrhaphy vs PN without. >= t1b, not separate in analyses.
Borghesi, 2013	Nonsystematic review (narrative)
Zhang, 2021	Better SR of Jian 2019 with quality assessment
Badalato, 2012	Included in SR of Jian 2019

Jang, 2016	Included in SR of Jian 2019
Weight, 2010	Included in SR of Jian 2019
Liu, 2017	Included in SR of Chan 2022
Shapiro, 2020	Included in SR of Chan 2022
Cazalas, 2021	Included studies with wrong comparisons

Literature search strategy

Algemene informatie

Richtlijn: Herziening Niercelcarcinoom	
Uitgangsvraag: Wat zijn de (on)gunstige effecten van partiële nefrectomie, totale nefrectomie, SABR, percutane ablatie patiënten met een niet-gemetastaseerd niercelcarcinoom tussen 4-7 cm?	
Database(s): Medline (OVID), Embase	Datum: 10-02-2022
Periode: >2000	Talen: Engels, Nederlands
Literatuurspecialist: Linda Niesink	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: → Voor deze vraag is gezocht op de elementen **cT1b** (in het groen) **niercelcarcinoom** (in het blauw), en **partiële nefrectomie** (in het oranje). → De genoemde sleutelartikelen van Mir (2017) en Correa (2019) zitten in de zoekopbrengst. De artikelen van Caputo (2017), Rembeyo (2020), Antonelli (2008) en Yang (2019) vallen er buiten op studiedesign. Zonder beperking op SR en RCT's zouden deze artikelen wel gevonden worden. → Resultaten staan in Rayyan.	
Te gebruiken voor richtlijnen tekst: In de databases Embase (via embase.com) en Medline (via OVID) is op 10-02-2022 met relevante zoektermen gezocht naar systematische reviews en RCT's over partiële nefrectomie bij patiënten met een cT1b niercelcarcinoom. De literatuurzoekactie leverde 106 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	26	19	27
RCTs	79	13	79
Totaal	105	32	**106**

Zoekstrategie

Database	Zoektermen		
Embase	*No.*	*Query*	*Results*
	#1	'renal cell carcinoma'/exp OR 'non clear cell renal cell carcinoma'/exp OR 'kidney tumor'/exp OR ((('kidney' OR 'renal' OR nephroid OR hypernephroid OR 'collecting duct') NEAR/3 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR mass*)):ti,ab,kw) OR ((grawitz* NEAR/3 (tumor* OR tumour*)):ti,ab,kw) OR hypernephroma*:ti,ab,kw OR 'hyper nephroma*':ti,ab,kw OR rcc:ti,kw OR mrcc:ti,kw OR nccrcc:ti,ab,kw OR ncrcc:ti,ab,kw	187739
	#2	t1b:ti,ab,kw OR ct1b:ti,ab,kw OR '7 cm':ti,ab,kw	31971
	#3	'partial nephrectomy'/exp OR 'nephron sparing surgery'/exp OR 'stereotactic body radiation therapy'/exp OR 'ablation therapy'/exp OR 'cryoablation'/exp OR 'microwave radiation'/exp OR 'enucleation'/exp OR (((stereotactic OR stereotaxic) NEAR/3 (radiation OR therap* OR radiotherap*)):ti,ab,kw) OR ((partial NEAR/3 (nephrectom* OR 'kidney resection')):ti,ab,kw) OR 'nephron sparing':ti,ab,kw OR 'percutaneous treatment':ti,ab,kw OR ablation:ti,ab,kw OR cryoablation:ti,ab,kw OR microwave:ti,ab,kw OR 'micro wave':ti,ab,kw OR enucleation:ti,ab,kw	296641
	#4	#1 AND #2 AND #3 AND ([english]/lim OR [dutch]/lim) AND [2000-2022]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	523
	#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR	786647

		database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
	#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3444120
	#7	#4 AND #5 **– SR's**	26
	#8	#4 AND #6 NOT #7 **– RCT's**	79
	#9	#8 OR #9	105
Medline (OVID)	1 exp Carcinoma, Renal Cell/ or exp Kidney Neoplasms/ or (('kidney' or 'renal' or nephroid or hypernephroid or 'collecting duct') adj3 (cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or mass*)).ti,ab,kf. or (grawitz* adj3 (tumor* or tumour*)).ti,ab,kf. or hypernephroma*.ti,ab,kf. or (RCC or MRCC or nccrcc or ncrcc).ti,ab,kf. (112726) 2 (t1b or ct1b or '7 cm').ti,ab,kf. (9072) 3 exp Radiosurgery/ or exp Radiofrequency Ablation/ or exp Cryosurgery/ or exp Microwaves/ or ((stereotactic or stereotaxic) adj3 (radiation or therap* or radiotherap*)).ti,ab,kf. or (partial adj3 (nephrectom* or 'kidney resection')).ti,ab,kf. or ('nephron sparing' or 'percutaneous treatment' or ablation or cryoablation or microwave* or 'micro wave*' or enucleation).ti,ab,kf. (211003) 4 1 and 2 and 3 (468) 5 limit 4 to ((english or dutch) and yr="2000 -Current") (409) 6 5 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (385) 7 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) (573135) 8 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (1351271) 9 6 and 7 (19) **– SRs** 10 (6 and 8) not 9 (13) **- RCTs** 11 9 or 10 (32)	

Bijlagen bij module 2

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Bied bij patiënten met gemetastaseerd heldercellig niercelcarcinoom met good risk kenmerken behandeling aan met sunitinib of pazopanib. In uitzonderingen kan er indicatie zijn voor combinatie behandeling. Bied in dergelijke situaties behandeling met pembrolizumab + axitinib of nivolumab + cabozantinib of Lenvatinib + pembrolizumab aan.	1-3 jaar	Geen effect / onduidelijk effect	Beschikbaarheid systeemtherapie Kennis van richtlijnmodule	Gebrek aan kennis van richtlijnmodule	Disseminatie module	NVU NIV (NVMO)	
Bied bij patiënten met gemetastaseerd heldercellig niercelcarcinoom met intermediair of ongunstige IMDC Risico score kenmerken	1-3 jaar	Geen effect / onduidelijk effect	Beschikbaarheid systeemtherapie Kennis van richtlijnmodule	Gebrek aan kennis van richtlijnmodule	Disseminatie module	NVU NIV (NVMO)	

behandeling met ipilimumab + nivolumab of pembrolizumab + axitinib of nivolumab + cabozantinib of Lenvatinib of pembrolizumab aan.							
Overweeg cabozantinib, sunitinib of pazopanib voor patiënten met intermediair of ongunstige IMDC Risico score kenmerken die een contra-indicatie voor immuuntherapie hebben.	1-3 jaar	Geen effect / onduidelijk effect	Beschikbaarheid systeemtherapie Kennis van richtlijnmodule	Gebrek aan kennis van richtlijnmodule	Disseminatie module	NVU NIV (NVMO)	
Registreer de IMDC Risico score (gunstig, intermediair, ongunstig) bij iedere patiënt met gemetastaseerd niercelcarcinoom in de conclusie van het multidisciplinair overleg.	1-3 jaar	Geen effect / onduidelijk effect	Beschikbaarheid systeemtherapie Kennis van richtlijnmodule	Gebrek aan kennis van richtlijnmodule	Disseminatie module	NVU NIV (NVMO)	

[1] **Barriëres kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.**

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables
Evidence table for systematic review of RCTs and observational studies (intervention studies)

Research question:
P: patients with metastatic clear cell renal carcinoma
I: immunotherapy + targeted therapy
C: sunitinib
O: progression-free survival (PFS), overall survival (OS), Quality of Life, adverse events

Only RCTs of which results for the selected outcomes were reported in the SR for all risk groups combined and for intermediate and poor risk groups (according to the International Metastatic RCC Database Consortium) are reported in this table. For other information, see Aldin, 2023.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Aldin, 2023 Only RCTs of which results for the selected outcomes were reported in the SR for all risk groups combined. Study characteristics and results are extracted	SR and meta-analysis of RCTs *Literature search up to 9 February 2022* **A**: NCT00979966 (Bergmann, 2020) **B**: NCT01024920 (Eisen, 2015) **C**: NCT00720941 (COMPARZ) (Motzer, 2013) **D**: NCT00732914 (SWITCH) (Eichelberg, 2015)	Inclusion criteria SR: RCTs, patients with metastatic RCC without previous systemic therapy, intervention targeted therapy, immunotherapy, interferon, interleukin, placebo, or any combinations	**A**: temsirolimus (25 mg, IV, once a week) **B**: nintedanib (200 mg, oral, twice/day) **C**: pazopanib (800 mg, oral, once/day) **D**: sorafenib (400 mg, oral, twice/day) **E**: everolimus (10 mg, oral, once/day) **F**: everolimus (10 mg, oral, once/day) **G**: cabozantinib (60 mg, oral, once/day) **H**: atezolizumab (1200 mg,	**A**: sunitinib (50 mg, oral, once/day) **B**: sunitinib (50 mg, oral, once/day) **C**: sunitinib (50 mg, oral, once/day) **D**: sunitinib (50 mg, oral, once/day) **E**: sunitinib (50 mg, oral, once/day) **F**: sunitinib (50 mg, oral, once/day) **G**: sunitinib (50 mg, oral, once/day) **H**: sunitinib (50 mg, oral, once/day)	<u>End-point of follow-up</u>: **A**: 12 months **B**: 36 months **C**: 67 months **D**: 48 months **E**: 56 months **F**: 24 months **G**: 60 months **H**: 33 months **I**: 33 months **J:** 31 months **K:** 27 months **L:** not reported **M:** 67 months **N:** 67 months **O:** 22 months	<u>Outcome measure-1</u> Defined as Overall survival Effect measure: HR [95% CI] **A**: 0.98 [0.31, 3.09] **B**: 0.92 [0.54, 1.56] **C**: 0.92 [0.79, 1.07] **F**: 1.12 [0.48, 2.60] **H**: 1.06 [0.65, 1.73] **I**: 1.30 [0.80, 2.12] **J:** 0.69 [0.59, 0.81] **K:** 0.91 [0.76, 1.08] **L:** 0.84 [0.47, 1.51] **M:** 0.66 [0.49, 0.88] **N:** 1.15 [0.88, 1.50]	<u>Risk of bias (high, some concerns or low):</u> Tool used by authors: RoB 2.0 tool **A**: High **B**: Some concerns **C**: Low **D**: High **E**: High **F**: Some concerns **G**: Some concerns **H**: Some concerns **I**: Some concerns **J:** Low **K:** Low **L:** Some concerns

from the SR (unless stated otherwise)	**E**: NCT00903175 (RECORD-3) (Motzer, 2014) **F**: NCT01108445 (ASPEN) (Armstrong, 2016) **G**: NCT01835158 (CABOSUN) (Choueiri, 2018) **H**: NCT01984242a (IMmotion150) (McDermott, 2018) **I**: NCT01984242b (IMmotion150) (McDermott, 2018) **J:** NCT02231749 (Checkmate 214) (Albiges, 2020) **K:** NCT02420821 (IMmotion 151) (Rini, 2021) **L:** NCT02761057 (SWOG 1500) (Pal, 2021) **M:** NCT02811861a (CLEAR) (Motzer, 2021) **N:** NCT02811861b (CLEAR) (Motzer, 2021) **O:** NCT02853331 (KEYNOTE-426) (Rini, 2021) **P:** NCT03141177 (CHECKMATE 9ER) (Choueiri, 2021)	Exclusion criteria SR: adjuvant setting, comparison between interleukin and interferon only *36 studies included in the SR; in 16 sunitinib was used as comparator* <u>Important patient characteristics at baseline</u>: <u>N, mean age (range) or mean (SD)(yrs)</u> **A**: 22 patients, I: 57.4 (29-85), C: 64.8 (46-80) **B**: 96 patients, I: 62 (42-86), C: 58 (29-79) **C**: 1110 patients, Group 1: 60.9 (10.89), Group 2: 61.2 (10.98) **D**: 365 patients, I: median	intravenous, every three weeks) **I**: atezolizumab (1200 mg, intravenous, every three weeks) + bevacizumab (15 mg/kg, intravenous, every three weeks) **J:** nivolumab (3 mg/kg, intravenous) + ipilimumab (1 mg/kg, intravenous), every 3 weeks for four doses (induction phase) followed by nivolumab montherapy (maintenance therapy) **K:** atezolizumab (1200 mg, intravenous) + bevacizumab (15 mg/kg, intravenous), once every 3 weeks **L:** cabozantinib (60 mg, oral, once/day) **M:** lenvatinib (20 mg, oral, once/day), pembrolizumab (200mg, intravenous, every 3 weeks) **N:** lenvatinib (18 mg, oral, once/day) + everolimus (5mg, oral, once/day)	**I**: sunitinib (50 mg, oral, once/day) **J:** sunitinib (50 mg, oral, once/day) **K:** sunitinib (50 mg, oral, once/day) **L:** sunitinib (50 mg, oral, once/day) **M:** sunitinib (50 mg, oral, once/day) **N:** sunitinib (50 mg, oral, once/day) **O:** sunitinib (50 mg, oral, once/day) **P:** sunitinib (50 mg, oral, once/day) **Q:** sunitinib (50 mg, oral, once/day)	**P:** 23 months **Q:** 40 months	**O:** 0.73 [0.60, 0.88] **P:** **Q:** Intermediate IMDC risk group 0.84 [0.65, 1.08]; poor IMDC risk group 0.60 [0.40, 0.91] No statistical pooling <u>Outcome measure-2</u> Defined as Quality of Life Effect measure: mean difference [95%CI] **C**: FACIT-F 9.00 [-9.86; 27.86] in favour of pazopanib (n=4) <u>Outcome measure-3</u> Defined as Serious Adverse Events (SAEs) Effect measure: RR [95% CI] **A**: 0.97 [0.48, 1.95] **B**: 0.91 [0.50, 1.66] **C**: 0.99 [0.87, 1.14] **D**: 1.08 [0.87, 1.34] **E**: 1.03 [0.88, 1.20] **F**: 0.79 [0.62, 1.00] **G**: 0.92 [0.68, 1.26] **H**: 1.28 [0.85, 1.93] **I**: 1.73 [1.19, 2.52] **J:** 1.40 [1.23, 1.59]	**M:** High **N:** High **O:** Low **P:** High **Q:** High

	Q: NCT02684006 JAVELIN renal 101 (Haanen, 2021) Study design: RCT parallel (for cross-over studies, only the first period was extracted by the reviewers) Setting and Country: **A**: 1 country (Germany), clinics, university hospitals (14 study locations) **B**: 5 countries (Hungary, Poland, Romania, Ukraine, UK), cancer centres, hospitals, university hospitals, research centres (15 study locations) **C**: 14 countries (Australia, Canada, China, Germany, Ireland, Italy, Japan, Republic of Korea, the Netherlands, Spain, Sweden, Taiwan, UK, USA), types of centres: not reported (227 study locations)	(range) 63 (39-84) yrs, C: (median, range) 65 (40-83) yrs **E**: 471 patients, I: median (range) 62 (20-89) yrs, C: median (range) 62 (29-84) yrs **F**: 108 patients, I: median (range) 64 (29-90) yrs, C: median (range) 59 (24-100) yrs **G**: 157 patients, I: median (range 63 (56-69) yrs, C: median (range) 64 (57-71) yrs **H**: 204 patients, I: median (range) 61 (27-81) yrs, C: median (range) 61 (25-85) yrs **I**: 202 patients, I: median (range) 62 (32-88) yrs, C: median (range) 61 (25-85) yrs **J:** 1096 patients, median (range) age I: 62 (26-85)	**O:** pembrolizumab (200 mg, intravenous, every 3 weeks for up to 35 cycles) + sxitinib (5 mg, oral, twice/day) **P:** nivolumab (240 mg, intravenous, every 2 weeks) + cabozantinib (40 mg, oral, once/day) **Q:** avelumab (10 mg/kg, intravenous, every 2 weeks) + axitinib (mg, oral, twice/day)			**K:** 1.11 [0.95, 1.31 **M:** 1.52 [1.27, 1.83] **N:** 1.39 [1.15, 1.68] **O:** 1.29 [1.07, 1.55] No statistical pooling Outcome measure-4 Defined as Progression-Free Survival (PFS) Effect measure: HR [95% CI] **A**: 1.76 [0.70, 4.44] **B**: 1.12 [0.70, 1.80] **C**: 1.05 [0.90, 1.22] **D**: 1.19 [0.93, 1.53] **E**: 1.40 [1.14, 1.71] **F**: 1.41 [0.87, 2.28] **G**: 0.48 [0.31, 0.74] **H**: 1.19 [0.82, 1.72] **I**: 1.00 [0.69, 1.45] **J:** 0.89 [0.76, 1.05] **K:** 0.83 [0.71, 0.98] **L:** 0.61 [0.37, 0.99] **M:** 0.39 [0.32, 0.48] **N:** 0.65 [0.53, 0.80] **O:** 0.68 [0.58, 0.80] **P:** 0.51 [0.41, 0.64] **Q:** Intermediate IMDC risk group 0.71 [0.58, 0.87]; poor IMDC risk group 0.45 [0.30, 0.67] No statistical pooling	

	D: 1 country (Germany), 1 urology clinic **E**: 19 countries (Argentina, Australia, Brazil, Canada, Denmark, France, Germany, Hong Kong, Italy, Republic of Korea, Mexico, the Netherlands, Peru, Spain, Taiwan, Thailand, Turkey, UK, USA), types of centres: cancer centres/institutes, hospitals, (84 study locations) **F**: 3 countries (Canada, UK, USA), types of centres: medical centres/agencies, clinics, hospitals, (18 study locations) **G**: 1 country (USA), types of centres: cancer centres/clinics, medical centres, hospitals (488 study locations) **H, I**: 9 countries (Czech Republic, France, Germany,	yrs, C: 62 (21-85) yrs **K:** 915 patients, median (range) age I: 62 (56-69) yrs, C: 60 (54-66) yrs **L:** 147 patients in 4 arms, median (range) age 66 (58-75) yrs (all participants), 90 patients (I: 44, C: 46) for interventions reported in this table **M:** 692 patients, median (range) age I: 64 (34-88) yrs, C: 61 (29-82) yrs **N:** 695 patients, median (range) age I: 62 (32-86) yrs, C: 61 (29-82) yrs **O:** 861 patients, median (range) age I: 62 (55-68) yrs, C: 61 (53-68) yrs **P:** 651 patients, median (range) age I: 62 (29-90)					

	Italy, Poland, Romania, Spain, UK, USA), types of centres: cancer centres, medical centres, hospitals, research institutions (45 study locations) **J:** 28 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Republic of Korea, Mexico, the Netherlands, Poland, Spain, Sweden, Taiwan, Turkey, UK USA), types of centres: not reported (190 study locations) **K:** 21 countries (Australia, Bosnia and Herzegovina, Brazil, Canada, Czech Republic, Denmark, France, Germany, Italy, Japan,	yrs, C: 61 (28-86) yrs **Q:** 886 patients, median (range) age I: 62 (29-83) yrs, C: 61 (27-88) yrs <u>*Sex (% male)*</u>*:* **A**: 73 **B**: 85 **C**: 73 **D**: 75 **E**: 73 **F**: 75 **G**: 78 **H**: 76 **I**: 76 **J:** 74 **K:** 73 **L:** 24(?) **M**: 77 **N:** 78 **O:** 73 **P:** 74 **Q:** 74 Groups comparable at baseline? Probably yes, randomized.					

	Republic of Korea, Mexico, Poland, Russian Federation, Singapore, Spain, Taiwan, Thailand, Turkey, UK USA), types of centres: cancer centres/institutes, medical centres, hospitals, university hospitals (154 study locations) **L:** 2 countries (Canada, U.S.A.), cancer centres, medical centres, hospitals, (597 study locations) **M, N:** 20 countries (Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Greece, Ireland, Israel, Italy, Japan, Republic of Korea, the Netherlands, Poland, Russian Federation, Spain, Switzerland, UK USA), types of centres: hospitals, university hospitals,						

	medical centres, cancer centres (183 study locations) **O:** 16 countries (not reported), types of centres: hospitals, cancer centres (129 study locations) **P:** 18 countries, (Argentina, Australia, Brazil, Chile, Czech Republic, Germany, Greece, Israel, Italy, Japan, Mexico, Poland, Romania, Russia, Spain, Turkey, UK, USA) **Q:** 21 countries (Australia, Austria, Belgium, Canada, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Mexico, the Netherlands, New Zealand, Romania, Russian Federation, Spain, Sweden, UK, USA), types of centres: hospitals, university hospitals, medical centres, centres/						

	institutes (280 study locations) <u>Source of funding and conflicts of interest:</u> **A**: Pfizer, Germany **B**: Quote: "Pfizer, Bayer and AstraZeneca, and travel funding for a conference from Novartis. MM and YS have received research funding from Boehringer Ingelheim. RJJ has received research funding from Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer and Roche. Funding for this study was provided by Boehringer Ingelheim." **C**: GlaxoSmithKline Pharmaceuticals and Novartis Pharmaceuticals **D**: Bayer, Pfizer, and Novartis **E**: Novartis, Pfizer, GlaxoSmithKline,						

	Amgen, Bayer AG/Onyx Pharmaceuticals, Genentech, ZymoGenetics **F**: Novartis and Pfizer **G**: Funder: National Cancer Institute (part of the National Institutes of Health); extensive declarations of interests **H, I**: "Prometheus Laboratories. M.B.A., Roche/Genentech, Novartis, Pfizer, Eisai, and Exelixis, F. Hoffmann-La Roche, AG (...)" "consulting/advisory role for Bristol-Myers Squibb, Merck, Roche/ Genentech, Pfizer, Exelixis, Novartis, Eisai, X4 Pharmaceuticals, and Array BioPharma" **J:** Bristol-Myers Squibb and ONO Pharmaceutical and						

	grants and personal fees from Pfizer, Novartis, Eisai, Exelixis, and Genentech/Roche **K:** Hoffmann–La Roche Ltd and Genentech Inc. **L:** National Institutes of Health and National Cancer Institute **M, N:** Eisai and Merck Sharp and Dohme **O:** Merck Sharp & Dohme **P:** Bristol-Myers Squibb and others **Q:** Pfizer and Merck						

Table of excluded studies

Reference	Reason for exclusion
Albiges, 2020	Included in Aldin 2023
Alam, 2020	Less comprehensive than Aldin 2023, some studies not over ccRCC
Atkins, 2021	No RCT, no comparison with sunitinib
Bedke, 2021	Guideline, not a study
Bedke, 2021	Guideline, not a study
Buti, 2020	Less methodological quality than Aldin 2023
Cao, 2020	Less comprehensive than Aldin 2023
Cella, 2019	Included in Aldin 2023
Choueiri, 2020	Included in Aldin 2023
Choueiri, 2021	Included in Aldin 2023
Elaidi, 2020	Less comprehensive than Aldin 2023
George, 2019	Included in Aldin 2023
Hahn, 2019	Less comprehensive than Aldin 2023
Heo, 2021	Wrong population, Less comprehensive than Aldin 2023
Hofmann, 2020	Wrong Intervention; VEGF-targeted therapies
Karner, 2019	Wrong population; VEGF-targeted treatment
Liu, 2021	Less comprehensive than Aldin 2023
Manz, 2020	Wrong comparison, Less comprehensive than Aldin 2023
McFarlane, 2020	Wrong Population, no comparison with sunitinib
Monteiro, 2020	Less comprehensive than Aldin 2023
Mori, 2021	Less comprehensive than Aldin 2023
Motzer, 2019	Included in Aldin 2023
Motzer, 2020	No comparison with sunitinib
Motzer, 2020	Included in Aldin 2023
Motzer, 2021	Included in Aldin 2023
Motzer,2020	Included in Aldin 2023
Powles, 2020	Included in Aldin 2023
Quhal, 2021	Less comprehensive than Aldin 2023
Quhal, 2021	Less comprehensive than Aldin2023; wrong outcome
Riaz, 2021	Less comprehensive than Aldin 2023
Rini, 2019	Included in Aldin 2023
Su, 2020	Less comprehensive than Aldin 2023
Sun, 2019	Wrong PICO; new alternative dosing schedule (2 weeks on/1 week off) of sunitinib with the traditional 4/2 schedule
Tomita, 2020	Wrong Intervention and Comparison; sunitinib followed by sorafenib and vice versa
Tremblay, 2019	Wrong comparison (everolimus)
Wang, 2019	Less comprehensive than Aldin 2023

Literature search strategy

Algemene informatie

Richtlijn: Herziening Niercelcarcinoom	
Uitgangsvraag: Wat zijn de (on)gunstige effecten van targeted therapy vergeleken met een combinatie van immuuntherapie en targeted therapy bij patiënten met gemetastaseerd niercelcarcinoom?	
Database(s): Medline (OVID), Embase	Datum: 12-07-2021
Periode: >2019	Talen: Engels, Nederlands

Literatuurspecialist: Linda Niesink
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.
Toelichting: → Voor deze vraag is gezocht op de elementen **gemetastaseerd** (in het groen) **niercelcarcinoom** (in het blauw), en **immuuntherapie óf targeted therapy** (in het oranje). → de genoemde sleutelartikelen van Choueiri (2021) en Motzer (2021) worden gevonden met de zoekstrategie. → resultaten staan in Rayyan.
Te gebruiken voor richtlijnen tekst: In de databases Embase (via embase.com) en Medline (via OVID) is op 12-07-2021 met relevante zoektermen gezocht naar systematische reviews en RCT's over immuuntherapie en targeted therapy bij patiënten met gemetastaseerd niercelcarcinoom. De literatuurzoekactie leverde 521 unieke treffers op.

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	125	89	135
RCTs	259	276	386
Totaal	384	365	**521**

Zoekstrategie

Database	**Zoektermen**		
Embase	*No.*	*Query*	*Results*
	#1	'renal cell carcinoma'/exp/mj OR 'clear cell renal cell carcinoma'/exp OR (((('kidney cell*' OR 'renal cell*' OR nephroid OR hypernephroid OR 'collecting duct') NEAR/3 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR mass*)):ti,kw) OR ((grawitz* NEAR/3 (tumor* OR tumour*)):ti,ab,kw) OR hypernephroma*:ti,ab,kw OR 'hyper nephroma*':ti,ab,kw OR rcc:ti,kw OR mrcc:ti,kw	50530
	#2	'metastasis'/exp/mj OR advanced:ti,ab,kw OR metastat*:ti,ab,kw	1140492
	#3	'targeted therapy'/exp OR 'molecularly targeted therapy'/exp OR ((targeted NEAR/3 therap*):ti,ab,kw) OR 'cabozantinib'/exp OR 'nivolumab'/exp OR 'lenvatinib'/exp OR 'pembrolizumab'/exp OR 'ipilimumab'/exp OR 'axitinib'/exp OR 'tivozanib'/exp OR 'avelumab'/exp OR cabozantinib:ti,ab,kw OR nivolumab:ti,ab,kw OR lenvatinib:ti,ab,kw OR pembrolizumab:ti,ab,kw OR ipilimumab:ti,ab,kw OR axitinib:ti,ab,kw OR tivozanib:ti,ab,kw OR avelumab:ti,ab,kw OR 'cancer immunotherapy'/exp OR 'immune checkpoint inhibitor'/exp OR	357328

		immunotherap*:ti,ab,kw OR 'immune therap*':ti,ab,kw OR 'immune checkpoint':ti,ab,kw	
	#4	#1 AND #2 AND #3 AND ([english]/lim OR [dutch]/lim) AND [2019-2021]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	1184
	#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	723324
	#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3278881
	#7	#4 AND #5 **– SR's**	125
	#8	#4 AND #6 NOT #7 **– RCT's**	259
	#9	#8 OR #9	384
Medline (OVID)	1 exp Carcinoma, Renal Cell/ or (('kidney cell*' or 'renal cell*' or nephroid or hypernephroid or 'collecting duct') adj3 (cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or mass*)).ti,kw. or (grawitz* adj3 (tumor* or tumour*)).ti,ab,kw. or hypernephroma*.ti,ab,kw. or (RCC or MRCC).ti,kw. (42401) 2 exp *Neoplasm Metastasis/ or (advanced or metastat*).ti,ab,kw. (701807)		

	3 exp Molecular Targeted Therapy/ or (targeted adj3 therap*).ti,ab,kw. or exp Nivolumab/ or exp Axitinib/ or exp Ipilimumab/ or nivolumab.ti,ab,kw. or lenvatinib.ti,ab,kw. or tivozanib.ti,ab,kw. or axitinib.ti,ab,kw. or exp *IMMUNOTHERAPY/ or (immune therap* or immunotherap* or immune checkpoint or cabozantinib or ipilimumab or pembrolizumab or tivozanib or avelumab).ti,ab,kw. (311736) 4 1 and 2 and 3 (4294) 5 limit 4 to ((english or dutch) and yr="2019 -Current") (1049) 6 5 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (998) 7 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) (490203) 8 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (2105819) 9 6 and 7 (89) **– SRs** 10 (6 and 8) not 9 (276) **- RCTs** 11 9 or 10 (365)

Bijlagen bij module 3

Implementatieplan

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Bespreek palliatieve behandeling met sunitinib bij een patiënt met een gemetastaseerd niet-heldercellig niercelcarcinoom als patiënt in afdoende conditie is voor palliatieve systeemtherapie.	1-3 jaar	Niet bekend, maar naar inschatting neutraal	bekendmaking richtlijn	Gebrek aan kennis over module	bekendmaken richtlijn	NVU, NVRO	
Maak bij patiënten met een gemetastaseerd papilliar niercelcarcinoom de afweging of er een meerwaarde is van	1-3 jaar	Niet bekend maar naar inschatting neutraal	bekendmaking richtlijn	-	bekendmaken richtlijn	NVU, NVRO	

cabozantinib boven sunitinib als er palliatieve systemische therapie gestart gaat worden.							

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

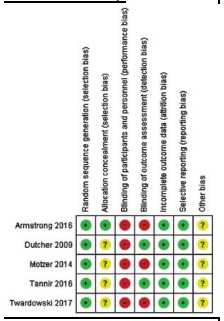
[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Risk of bias

Study	Appropriate and clearly focused question?[1]	Comprehensive and systematic literature search?[2]	Description of included and excluded studies?[3]	Description of relevant characteristics of included studies?[4]	Appropriate adjustment for potential confounders in observational studies?[5]	Assessment of scientific quality of included studies?[6]	Enough similarities between studies to make combining them reasonable?[7]	Potential risk of publication bias taken into account?[8]	Potential conflicts of interest reported?[9]
Osterman, 2020	Yes. Research question and inclusion criteria were clearly described.	Yes. Medline and EMBASE were searched, and search period and strategy were reported.	Yes. Reasons for the excluded studies were reported.	Yes. Characteristics were presented.	Not applicable.	Yes. Risk of bias was assessed.	Yes. Clinical and statistical heterogeneity were considered. No meta-analyses were performed because of the heterogeneity.	Yes. Authors stated that Based on the inclusion of multiple negative studies within this review, we do not suspect that publication bias had a significant impact on our results or conclusions.	No. Source of funding not indicated for the included studies.

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Osterman, 2020 study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs *Literature search up to [month/year]* June 2019 **A**: Armstrong, 2016 **B**: Motzer, 2014 **C**: Tannir, 2016 <u>Study design</u>: **A:** multicentre, open-label, randomised phase 2 trial **B:** open-label, randomized, multicenter, phase II **C:** Randomized Multicenter Phase 2 Trial <u>Setting and Country</u>: **A:** 17 centres in the USA, Canada, and the UK	Inclusion criteria SR: • Randomized controlled trials (RCTs). • Single-arm phase II–IV trials. • Prospective analyses of expanded access programs. • Studies focused on non-clear cell renal cell carcinoma (nccRCC). • Subtypes included: papillary RCC, chromophobe RCC, collecting duct RCC, translocation RCC, medullary RCC. • Studies evaluating	Describe intervention: **A**: Everolimus 10 mg once daily **B**: Everolimus 10 mg daily continually **C**: Everolimus 10 mg/d orally	Describe control: **A**: Sunitinib 50 mg once daily, for treatment cycles of 4 weeks on treatment and 2 weeks off treatment **B**: Sunitinib 50 mg daily in a schedule of 4 weeks on followed by 2 weeks off **C**: Sunitinib 50 mg/d orally for 4 wk on and 2 wk off.	<u>End-point of follow-up</u>: **A**: 24 months after study closure, **B**: Not reported **C**: median follow-up of 23.6 mo (95% confidence interval [CI], 15.7–30.2). <u>For how many participants were no complete outcome data available?</u> (intervention/control) **A: I** 13 participants (22%) C 10 participants (20%) **B**: I 0 participants (0%) C 1 participants (1%) **C**: I 2 participants (5.3%) C 1 participant (2.9%)	<u>Outcome measure-1</u> Progression free survival Effect measure: RR, RD, mean difference [95% CI]: **A**: I 5.6 (80% CI 5.5–6.0) C 8.3 (80% CI 5.8–11.4) HR 1.41 (80% CI 1.03–1.92) **B**: I 5.1 (2.6–7.9) C 7.2 (5.4–13.8) HR 1.5 (95% CI 0.9–2.8) **C**: I 4.1 (2.7–10.5) C 6.1 (4.2–9.4) <u>Outcome measure-2</u> Overall survival **A:** I 13.2 (9.7 – 37.9) C 31.5 (14.8 – NR) HR 1.12 (0.7 – 2.1) **B:** **C:** I 14.9 (8.0 – 23.4) C 16.2 (14.2 – NR) <u>Outcome measure-3</u> Quality of life **A:** I the median FACT-KSI score was 47·5 (IQR 23–59); C 45 (27–56) **B:** EORTC QLQ-C30 global health status scores, fatigue scores, and	<u>Risk of bias (high, some concerns or low):</u>  <u>Facultative</u>: Brief description of author's conclusion *This systematic review supports current consensus guidelines recommending sunitinib or enrollment in a clinical trial as first-line treatment options for nccRCC, but also suggests a more nuanced approach to management and new options for therapy such as immune checkpoint*

	B: 83 sites in 19 countries **C:** to 10 countries worldwide in approximately 50 to 75 sites <u>Source of funding and conflicts of interest:</u> [commercial / non-commercial / industrial co-authorship]	systemic treatment options for locally advanced or metastatic nccRCC. Exclusion criteria SR: • Phase I trials. • Retrospective analyses. • Case series, case reports. • Meta-analyses and reviews. • Studies that did not report results specifically for nccRCC patients. • Studies with fewer than 10 nccRCC patients. • Studies evaluating surgical or radiation therapy. • Multiple publications reporting on the same cohort (only the most				physical functioning scores showed no significant difference between the two arms in both TDD and the longitudinal analysis. **C:**Not reported <u>Outcome measure-4</u> Complications (Any grade 3 or 4 AE) **A:** Everolimus 34 (60%) patients sunitinib 40 (78%) patients **B:** Everolimus (14; 14%) sunitinib (10; 9%) **C:** Everolimus 19 of 35 patients (54%) and in sunitinib 29 of 33 patients (88%)	*inhibition. All patients with locally advanced or metastatic nccRCC should have genetic and molecular sequencing to identify those that may benefit from targeted therapies.*

		recent publication was included). *3 studies included* <u>Important patient characteristics at baseline</u>: <u>N, mean age</u> **A**: 108 patients, 61.5 yrs **B**: 471 patients, 62 years **C**: 68 patients, 59 years <u>*Sex*</u>*:* **A**: 75% Male **B**: 73% Male **C**: 63% Male Groups comparable at baseline? yes					

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies [cohort studies, case-control studies, case series])[1]

Research question:

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Choueiri et al., 2020	Type of study: Randomized controlled trial (Phase 3) Setting and country: Multicenter study, 32 centers across 7 countries Funding and conflicts of interest: Funded by AstraZeneca, no significant conflicts of interest	Inclusion criteria: MET-driven PRCC, measurable lesions, no prior treatment with MET or sunitinib inhibitors Exclusion criteria: Prior sunitinib or MET inhibitor therapy N total at baseline: 60 patients Intervention: 33 Control:27 Important prognostic factors[2]: *Median age: 62 (23-78)* *I: 60 (23-78) years* *C: 65 (31-77) years*	Describe intervention (treatment/procedure/test): Savolitinib 600 mg once daily	Describe control (treatment/procedure/test): Sunitinib 50 mg once daily for 4 weeks on, 2 weeks off	Length of follow-up: Study terminated early; median follow-up not fully specified Loss-to-follow-up: Intervention: N (%) 1 (2.7%) Reasons (describe) One patient withdrew consent after randomization. Control: N (%) 3 (6.5%) Reasons (describe) Three patients discontinued due to adverse events. Incomplete outcome data: Intervention: N (%) 2 (5.4%) Reasons (describe) Two patients were lost to follow-up before the first assessment. Control: N (%)4 (8.7%) Reasons (describe) Four patients had incomplete data due to withdrawal	Outcome measures and effect size (include 95%CI and p-value if available): PFS: savolitinib 7.0 (2.8-NC) Sunitinib 5.6 (4.1-6.9); HR (95% CI): 0.71 (0.37-1.36) OS: Not reached for savolitinib vs. 13.2 (7.6-NC) months for sunitinib; HR (95% CI): 0.51 (0.21-1.17) AEs: Grade 3 or higher AEs in 42% for savolitinib, 81% for sunitinib	Limitations Premature termination of the study and the limited number of patients randomized are key limitations of this study and make definitive conclusions on safety and efficacy difficult to draw.

		Sex: *I: 29 (88) M* *C: 17 (63) M* Groups comparable at baseline? yes			from the study or adverse events.		
Pal et al., 2021	Type of study: Randomized controlled trial (Phase 2) Setting and country: Conducted at 65 centers in the US and Canada Funding and conflicts of interest: Supported by NIH/National Cancer Institute, conflicts reported by some authors	Inclusion criteria: Advanced PRCC, up to one prior therapy Exclusion criteria: Untreated brain metastases N total at baseline:147 46 sunitinib, 44 cabozantinib, 29 savolitinib, 28 crizotinib) Important prognostic factors[2]: *Median age: 66 (58-75)* *I:* Cabozantinib *65 (58,75) years* *Crizotinib 68 (61,75)* *Savolitinib 67 (58,72)* *C: 65 (58-73)* *Sex: 112 (76%)* *I:* Cabozantinib *36 (82%)*	Describe intervention (treatment/procedure/test): Cabozantinib 60 mg oral daily with dose reductions to 40 mg and 20 mg permitted Crizotinib 250 mg twice daily with dose reductions to 200 mg twice daily and 250 mg once daily permitted Savolitinib 600 mg daily with dose reductions to 400 mg and 200 mg oral daily permitted	Describe control (treatment/procedure/test): Sunitinib 50 mg once daily for 4 weeks on, 2 weeks off with dose reductions to 37.5 mg and 25 mg permitted	Length of follow-up: Savolitinib arm halted early due to futility Loss-to-follow-up: Intervention: N (%)2 (4.5%) Reasons (describe) Two patients discontinued due to adverse events. Control: N (%) 3 (6.5%) Reasons (describe) Three patients withdrew consent. Incomplete outcome data: Intervention: N (%)1 (2.3%) Reasons (describe) One patient had missing data due to a delay in follow-up. Control: N (%) 2 (4.3%) Reasons (describe) Two patients had incomplete data due to treatment discontinuation.	Outcome measures and effect size (include 95%CI and p-value if available): PFS: cabozantinib 9.0 months (95% CI: 5.6–12.4) Crizotinib 2.8 (2.6-3.6) savolitinib 3.0 (2.8-7.2) months sunitinib 5.6 (2.9-6.7) months OS: cabozantinib 20 months (95% CI: 11.3–NR) Crizotinib 19.9 (11.2-NR) savolitinib 11.7 (6.7-28.9) months sunitinib 16.4 (12.8-21.6) months AEs: Grade 3 or 4 AEs in 32 (74%) for Cabozantinib; 10 (37%) for Crizotinib; 11(39%) for savolitinib, 31 (68%) for sunitinib	

		Crizotinib 22 (79%) Savolitinib 19 (66%) *C: 35 (76%)* Groups comparable at baseline? yes					
Bergmann 2020	Type of study: A Randomized Phase IIa Trial Setting and country: Multicenter study conducted in Germany and Austria (CESAR and IAGN societies) Funding and conflicts of interest: Supported by a grant from Pfizer Germany; no major conflicts reported.	Inclusion criteria: Patients with histologically confirmed advanced non-clear cell renal cell carcinoma (nccRCC), including those with sarcomatoid features (>50% sarcomatoid component). Exclusion criteria: Patients with previous treatment with VEGF or mTOR inhibitors, untreated brain metastases, and severe comorbidities. N total at baseline:22 Intervention: 12 Control: 10	Describe intervention (treatment/procedure/test): Temsirolimus: 25 mg intravenously once weekly	Describe control (treatment/procedure/test): Sunitinib: 50 mg orally, daily for 4 weeks on, 2 weeks off	Length of follow-up: Median follow-up duration of 9.3 months Loss-to-follow-up: Intervention: N (%) 0 Reasons (describe) No patients were lost to follow-up. Control: N (%) 1 (10%) Reasons (describe) One patient discontinued due to treatment-related adverse events. Incomplete outcome data: Intervention: N (%) 1 (8.3%) Reasons (describe) One patient was unable to complete the treatment due to disease progression. Control: N (%) 1 (10%) Reasons (describe) One patient discontinued	Outcome measures and effect size (include 95%CI and p-value if available): Progression-free survival (PFS): Median PFS was 9.3 months for temsirolimus vs. 13.2 months for sunitinib (HR: 1.64, 95% CI: 0.65–4.18, p = 0.20). Overall survival (OS): Median OS was 19.4 months for temsirolimus vs. 19.8 months for sunitinib (HR 0.98, 95% CI: 0.31–3.09). Adverse events (AEs): Serious AEs occurred in 91.7% of temsirolimus patients and 100% of sunitinib patients. The most common AEs included cytopenia, gastrointestinal events, and infections.	The recruitment rate was low and the trial had to be ended prematurely.

		Important prognostic factors[2]: age ± SD: 60.8 (29–85) I: 59.5 years (29–85) C: 65.5 (46–80) *Sex:* *I: 67% male (8/12)* *C: 80% male (8/10)* Groups comparable at baseline? yes			treatment due to intolerable side effects.		

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Risk of bias table for intervention studies (randomized controlled trials; based on Cochrane risk of bias tool and suggestions by the CLARITY Group at McMaster University)

Research question: Is immunotherapy and/or targeted therapy as a first-line systemic therapy preferred to sunitinib in patients with metastatic non-clear cell renal cell carcinoma?

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?**	**Was the allocation adequately concealed?**	**Blinding: Was knowledge of the allocated interventions adequately prevented?**	**Was loss to follow-up (missing outcome data) infrequent?**	**Are reports of the study free of selective outcome reporting?**	**Was the study apparently free of other problems that could put it at a risk of bias?**	**Overall risk of bias** **If applicable/necessary, per outcome measure**

			Were patients blinded? **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?**				
Pal, 2020	Probably yes; Reason: Randomization was dynamically balanced on two stratification factors.	Probably no; Reason: not reported	Definitely no; Reason: open-label	Probably yes; Reason: No loss to follow-up reported.	Probably yes; Reason: All relevant outcomes were reported.	Probably yes; Reason: No other problems noted.	**Some concerns**
Bergman, 2020	Probably no; Patients who met the eligibility criteria were randomly assigned 1: 1	Probably no; Not reported	Definitely no; Reason: open-label	Probably yes; Reason: No loss to follow-up reported.	Probably yes; Reason: All relevant outcomes were reported.	Probably no; Trial had to be terminated due to low recruitment and the small numbers.	**High**
Choueiri, 2020	Probably no; Patients were randomized in a 1:1 ratio	Probably no; Not reported	Probably no; Open label sponsor-blinded study; blinded independent central review;	Definitely yes 1 Lost to follow-up in savolitinib	Probably yes; Reason: All relevant outcomes were reported.	Probably no; Premature termination of the study and the limited number of patients randomized	**High**

Table of excluded studies

Authors	Reason
Brown, 2022	Better systematic review available
Bellmunt, 2013	Narrative review
Bellmunt, 2013	Narrative review
Bitting, 2011	Narative review
Buti, 2021	Does not comply with PICO (clear cell)
Chahoud, 2020	Does not comply with PICO (No comparison with sunitinib)
Choueiri, 2021	Post hoc from JAVELIN Renal 101 trial
de Vries-Brilland, 2021	Narrative review
Fernandez-Pello, 2017	Better systematic review available
Graham, 2022	Retrospective study -VEGF targeted therapy, mTOR targeted therapy, ICI-based therapy-
Gulati, 2020	Narrative review
Hutson, 2021	Does not comply with PICO (non comparative study, single arm phase II Lenvatinib+everolimus)
Jung, 2018	Does not comply with PICO (No RCT, single arm, no comparison with sunitinib)
Martin, 2019	Retrospective study
McDermott, 2021	Does not comply with PICO (No RCT, single arm, no comparison with sunitinib)
Palma Dos Reis, 2022	Does not comply with PICO (no comparison with sunitinib)
Papanikolaou, 2020	Does not comply with PICO (wrong population, retrospective studies included)
Park, 2018	Does not comply with PICO (no comparison with sunitinib, Phase II Axitinib)
Puente, 2016	Summary of an expert review panel meeting
Sepe, 2021	Narrative review
Tachibana, 2021	Does not comply with PICO (no comparison with sunitinib, retrospective of 30 patients)
Tannir, 2012	Does not comply with PICO (no comparison, single arm Phase II with sunitinib)
Tannir, 2021	Post hoc of CheckMate 214
Tazi, 2011	Narrative review
Twardowski, 2017	Does not comply with PICO (no comparison, single arm Phase II with sunitinib)
Vogelzang, 2020	Does not comply with PICO (No RCT, single arm, no comparison with sunitinib)
Voss, 2016	Does not comply with PICO (no comparison with sunitinib, Phase II, Everolimus Plus Bevacizumab)

Literature search strategy

Richtlijn: Herziening Niercelcarcinoom	
Uitgangsvraag: Wat is de optimale eerstelijns systeemtherapie bij patiënten met gemetastaseerd niet-heldercellig niercelcarcinoom?	
Database(s): Medline (OVID), Embase	Datum: 31-12-2022
Periode: >2011	Talen: Engels, Nederlands
Literatuurspecialist: Linda Niesink	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: → Voor deze vraag is gezocht op de elementen **gemetastaseerd, niet-heldercellig** (in het groen) **niercelcarcinoom** (in het blauw), en **immuuntherapie óf targeted therapy** (in het oranje). → Resultaten staan in Rayyan.	
Te gebruiken voor richtlijnen tekst: In de databases Embase (via embase.com) en Medline (via OVID) is op 04-01-2022 met relevante zoektermen gezocht naar systematische reviews en RCT's over immuuntherapie en/of targeted therapy bij patiënten met gemetastaseerd niet-heldercellig niercelcarcinoom. De literatuurzoekactie leverde 51 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	15	13	17
RCTs	32	15	34
Totaal	47	28	**51**

Zoekstrategie

Database	**Zoektermen**		
Embase	*No.*	*Query*	*Results*
	#1	'renal cell carcinoma'/exp OR 'non clear cell renal cell carcinoma'/exp OR ((('kidney cell*' OR 'renal cell*' OR nephroid OR hypernephroid OR 'collecting duct') NEAR/3 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR mass*)):ti,ab,kw) OR ((grawitz* NEAR/3 (tumor* OR tumour*)):ti,ab,kw) OR hypernephroma*:ti,ab,kw OR 'hyper nephroma*':ti,ab,kw OR rcc:ti,kw OR mrcc:ti,kw OR nccrcc:ti,ab,kw OR ncrcc:ti,ab,kw	77420
	#2	('metastasis'/exp OR 'advanced cancer'/exp OR advanced:ti,ab,kw OR metastat*:ti,ab,kw) AND ('non clear cell renal cell carcinoma'/exp OR 'non clear':ti,ab,kw OR nccrcc:ti,ab,kw OR ncrcc:ti,ab,kw)	748

	#3	'targeted therapy'/exp OR 'molecularly targeted therapy'/exp OR ((targeted NEAR/3 therap*):ti,ab,kw) OR 'cabozantinib'/exp OR 'nivolumab'/exp OR 'lenvatinib'/exp OR 'pembrolizumab'/exp OR 'ipilimumab'/exp OR 'axitinib'/exp OR 'tivozanib'/exp OR 'avelumab'/exp OR cabozantinib:ti,ab,kw OR nivolumab:ti,ab,kw OR lenvatinib:ti,ab,kw OR pembrolizumab:ti,ab,kw OR ipilimumab:ti,ab,kw OR axitinib:ti,ab,kw OR tivozanib:ti,ab,kw OR avelumab:ti,ab,kw OR 'cancer immunotherapy'/exp OR 'immune checkpoint inhibitor'/exp OR immunotherap*:ti,ab,kw OR 'immune therap*':ti,ab,kw OR 'immune checkpoint':ti,ab,kw	382843
	#4	#1 AND #2 AND #3 AND ([english]/lim OR [dutch]/lim) AND [2011-2022]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	157
	#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	786647
	#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3444120
	#7	#4 AND #5 **– SR's**	15
	#8	#4 AND #6 NOT #7 **– RCT's**	32
	#9	#8 OR #9	47

Medline (OVID)	1 exp Carcinoma, Renal Cell/ or (('kidney cell*' or 'renal cell*' or nephroid or hypernephroid or 'collecting duct') adj3 (cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or mass*)).ti,ab,kf. or (grawitz* adj3 (tumor* or tumour*)).ti,ab,kf. or hypernephroma*.ti,ab,kf. or (RCC or MRCC or nccrcc or ncrcc).ti,ab,kf. (54683) 2 (exp Neoplasm Metastasis/ or (advanced or metastat*).ti,ab,kf.) AND ('non clear' or nccrcc or ncrcc).ti,ab,kf. (326) 3 exp Molecular Targeted Therapy/ or (targeted adj3 therap*).ti,ab,kf. or exp Nivolumab/ or exp Axitinib/ or exp Ipilimumab/ or nivolumab.ti,ab,kf. or lenvatinib.ti,ab,kf. or tivozanib.ti,ab,kw. or axitinib.ti,ab,kw. or exp IMMUNOTHERAPY/ or (immune therap* or immunotherap* or 'immune checkpoint' or cabozantinib or ipilimumab or pembrolizumab or tivozanib or avelumab).ti,ab,kf. (474659) 4 1 and 2 and 3 (161) 5 limit 4 to ((english or dutch) and yr="2011 -Current") (138) 6 5 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (134) 7 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) (565255) 8 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (1341657) 9 6 and 7 (13) **– SRs** 10 (6 and 8) not 9 (15) **- RCTs** 11 9 or 10 (28)

Bijlagen bij module 4

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Bespreek de voor- en nadelen (uitstel systemische behandeling, mogelijke overlevingswinst versus invasieve behandeling oligometastasen) met de patiënt van de lokale behandeling van oligometastasen. Overweeg focale therapieën, afhankelijk van de conditie en comorbiditeit van patiënt, lokalisatie van metastasen, aantal metastasen en	1-3 jaar	Niet bekend, maar naar inschatting neutraal	bekendmaking richtlijn	Gebrek aan kennis over module	bekendmaken richtlijn	NVU, NVRO	

persoonlijke voorkeuren.							
Overweeg metastasectomie bij patiënten met metachrone oligometastasen op basis van mogelijke overlevingswinst en eventueel uitstel van systemische therapie. Bespreek hierbij met de patiënt de voor- en nadelen van een invasieve behandeling in vergelijking met een afwachtend beleid.	1-3 jaar	Niet bekend maar naar inschatting neutraal	bekendmaking richtlijn	-	bekendmaken richtlijn	NVU, NVRO	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence table for intervention studies

Research question: Which treatment (surgical metastasectomy, SBRT, ablation) is best applied to patients with a) synchronous oligometastases / b) metachronous oligometastases?

Met opmerkingen [JB1]: We hebben bij de 1e uitgangsvragen besloten te spreken/noteren 'percutane ablatie' is dit bij deze uitgangsvraag niet van toepassing?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Alt, 2011	Type of study: Retrospective study Setting and country: Mayo Clinic, US Funding and conflicts of interest: Source of funding not reported. The authors made no disclosures for conflicts of interest	Inclusion criteria Patients who underwent radical nephrectomy for pathologically confirmed RCC who were diagnosed with multiple metastases either at the time of or after nephrectomy Exclusion criteria Not reported N total at baseline: Intervention: 125 Control: 762 Important prognostic factors[2]: *Median age (range)* *I: 62 (41-85)* *C: 63 (21-92)* *Sex:* *I: 69.6% M* *C: 69.5% M* *Synchronous metastases* *I:73 (58.4%)* *C: 426 (55.9%)* Groups not comparable	Complete surgical resection	No complete surgical resection	Length of follow-up: Up to 10 years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Median overall survival (converted to months) I: 48 months C: 15.6 months P<0.001	Author's conclusion The current results indicated that complete resection of multiple RCC metastases may be associated with longterm survival and should be considered when technically feasible in appropriate surgical candidates. Remarks - Selection bias

Dragomir, 2020	Type of study: Retrospective study Setting and country: Canadian Kidney Cancer information system database (multicentre collaboration of 16 academic hospitals in 6 Canadian provinces) Funding and conflicts of interest: Source of funding and conflicts of interest not reported.	Inclusion criteria: Patients diagnosed with metastatic renal cell carcinoma with prior nephrectomy Exclusion criteria: Patients receiving a first incomplete metastasectomy N total at baseline: Intervention: 229 Control: 803 Important prognostic factors[2]: *Median age (IQR)* *I: 62 (55-68)* *C: 63 (57-70)* *Sex:* *I:78.2 % M* *C: 75.2% M* *Synchronous metastases* *I: 28.8%* *C: 30.4%* After matching, baseline characteristics were well balanced between groups	Complete metastasectomy: surgical resection of all visible metastases present at the time of surgery	No metastasectomy: resection of part of the metastases without a curative intent	Length of follow-up: 5 years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Overall survival (median and IQR) I: 81 months (58 to NR) C: 61 months (26 to NR) P=0.0001 Time to first-line targeted treatment during (median and IQR) I: 49 months (14-NR) C: 38 months (11-66) P=0.0057	Author's conclusion: Patients who underwent complete metastasectomy have a longer overall survival and a longer time to initiation of targeted therapy compared to patients not receiving metastasectomy. These findings should support aggressive resection of metastasis in selected patients. Remarks: - Selection bias
Fares, 2019	Type of study: Retrospective study (propensity score-matched analysis) Setting and country:	Inclusion criteria: - Patients with clear cell histology and absence of sarcomatoid or rhabdoid features	Complete metastasectomy	No metastasectomy	Length of follow-up: Median of 70.4 months Loss-to-follow-up: Not reported	Overall survival I: 98.3 months C: 40.5 months HR=0.24, 95%CI 0.11–0.53 p< 0.0001	Author's conclusion After matching for age, gender and IMDC, we found CM impacts on OS and also diminishes the need for systemic treatment.

	AC Camargo Cancer Center, Brazil Funding and conflicts of interest: No financial support was necessary for this study. None of the authors have any conflicts of interest.	who underwent previous nephrectomy - Patients who underwent complete metastasectomy and patients treated without metastasectomy and with targeted therapy alone Exclusion criteria: Not reported. N total at baseline: Intervention: 37 Control: 37 Important prognostic factors[2]: *Mean age (SD)* *I: 55.92 (11%)* *C: 57.38 (11%)* *Sex:* *I: 68% M* *C: 76% M* *Synchronous metastases* *I: 14 (37%)* *C: 7 (19%)* Groups not comparable			Incomplete outcome data: Not reported		Survival benefit was confirmed for favourable/intermediate IMDC but not for the poor IMDC prognostic model. Remarks: - Retrospective, non-randomised nature - Small sample size
Ishihara, 2020	Type of study: Retrospective study Setting and country: Tokyo Women's Medical University, Japan Funding and	Inclusion criteria Patients diagnosed with metastatic RCC (mRCC) Exclusion criteria - Registered on clinical trials - Undergone	Complete metastasectomy	Incomplete metastasectomy Without metastasectomy	Length of follow-up: Median of 25.3 months Loss-to-follow-up: Patients lost to follow-up were censored at the time of last contact.	Overall survival I: NR (121.9 to NR) C1: 81.5 months (44.6 to NR) C2: 28.1 months (22.6 to 41.5) P<0.0001	Author's conclusion MS, especially cMS improved survival in selected patients with mRCC in the postcytokine therapy era. In addition, MS still plays a significant role in the current systemic therapy.

	conflicts of interest: This study did not receive any funding. Tsunenori Kondo received honoraria from Pfizer, Novartis, and Ono Pharmaceutical. All other authors have no conflict of interest to declare.	maintenance dialysis - Kidney transplant - Administered first-line ipilimumab and nivolumab as systematic therapy - Missing eligible data N total at baseline: Intervention: 45 Control: C1 Incomplete: 53 C2 Without: 216 Important prognostic factors[2]: *Median age (IQR)* *I: 65.0 (57.0–68.5)* *C1: 61 (55.5–65)* *C2: 66.0 (57.3–72.0)* *Sex:* *I: 73.3% M* *C1: 71.7% M* *C2: 66.7% M* *Synchronous metastases* *I: 8 (17.8)* *C1: 27 (50.9%)* *C2: 126 (58.3%)* Groups not comparable			Incomplete outcome data: Patients with missing data were excluded.		Remarks: - Small sample size - Patients who underwent MS could have inherently favourable outcome - Relatively short follow-up duration
Kim, 2019	Type of study: Retrospective study (propensity score-matched analysis) Exclusion criteria:	Inclusion criteria: Patients with metastatic renal cell carcinoma	Metastasectomy	No metastasectomy	Length of follow-up: Median of 143.3 months Loss-to-follow-up: Not reported	Overall survival I: 32.0 months C: 12.8 months P<0.001	Author's conclusion The study showed a significantly beneficiary role of metastasectomy according to various

	Setting and country: AC Camargo Cancer Center, Brazil Funding and conflicts of interest: No financial support was necessary for this study. None of the authors have any conflicts of interest.	- Non-complete history of survival outcomes in the National Cancer Registry Database - Non-complete surgical records concerning metastasectomy or nephrectomy - Age <19 years N total at baseline: Intervention: 83 Control: 190 Important prognostic factors[2]: *Median age (range)* *I: 52 (22–78)* *C: 58 (10–76)* *Sex:* *I: 80.7% M* *C: 79.0% M* *Synchronous metastases* *I: 37 (44.6%)* *C: 124 (65.3%)* Groups not comparable			Incomplete outcome data: Not reported		metastatic states in survival gains with regards to mRCC and found that liver metastasis was the most unfavorable factor in metastasectomy in mRCC. Remarks: - Retrospective, single-center design - Low number of cases - Lack of consideration of the number of metastatic lesions within the metastatic organs, and the sizes or total sum of the metastatic lesions, representing the overall tumor burden - Derivation of results over an extended period - Baseline general performance status and underlying disease were not considered thoroughly
Kwak, 2007	Type of study: Retrospective study Setting and country: Korea Funding and conflicts of interest: Source of funding and	Inclusion criteria Patients with metastatic RCC who had not received immunotherapy (all patients did not meet the criteria for receiving immunotherapy or	Metastasectomy	Nonmetastasectomy	Length of follow-up: I: 36.5 months (4.0 to 182.7 months) C: 8.4 months (0.9 to 63.7 months) Loss-to-follow-up: Not reported	Median overall survival I: 36.5 months (4.0 to 182.7 months) C: 8.4 months (0.9 to 63.7 months) P<0.001	Author's conclusion Our findings suggest that for the management of metastatic renal cell carcinoma, complete surgical resection of the metastatic lesions may prolong survival even in patients with some poor prognostic

	conflicts of interest not reported.	refused receiving immunotherapy) Exclusion criteria - Not undergone radical nephrectomy - Metastasectomy was incomplete N total at baseline: Intervention: 21 Control: 41 Important prognostic factors[2]: *Median age (range)* *I: 60 (38–79)* *C: 61 (31–79)* *Sex:* *I: 90.5 % M* *C: 82.9% M* Groups not comparable at baseline.			Incomplete outcome data: Not reported		factors who cannot or are not willing to receive systemic therapy. Remarks: - Clinical experience one centre - Data depends on medical records - Observer bias
Li, 2018	Type of study: Retrospective chart-review analysis Setting and country: Taichung Veterans General Hospital, Taiwan Funding and conflicts of interest: This research was supported by the Ministry of Science and Technology of the	Inclusion criteria Consecutive metastatic renal cell carcinoma patients who had received at least one line of targeted therapy Exclusion criteria Incomplete data or loss to follow-up N total at baseline: Intervention: 26 Control: C1 incomplete: 23	Complete resection	Incomplete resection Without resection (only targeted therapy)	Length of follow-up: I: 41.9 months (23.8-63.2 months) C1: 41.3 months (24.9-50.7) C2: 13.4 months (8.3-31.8 months) Loss-to-follow-up: Patients loss to follow-up were excluded Incomplete outcome data: Patients with incomplete data were excluded	Overall survival (converted to months) I: 60.6 months C1: 42 months C2: 28.8 months	Author's conclusion Complete resection of metastatic sites for MRCC patients, combined with targeted therapy, could provide better overall survival rates than targeted therapy alone. Poor MSKCC risk is still correlated to a poor outcome in the current targeted therapy era. Remarks - Selection bias - Small patient numbers - Targeted treatment not identical

	Republic of China, Grant number MOST 105-2628-B-075A-001-MY3. All authors declare no conflicts of interest regarding this study.	C2 without: 75 Important prognostic factors[2]: *Median age (IQR)* *I: 59.5 (56-65.3)* *C1: 56.0 (0.6-62)* *C2: 58.0 (59.5-68)* *Sex:* *I: 65.4% M* *C1: 87.0% M* *C2: 65.3% M* Groups not comparable					
Liu, 2021	Type of study: Retrospective study Setting and country: Sun Yat-sen University Cancer Center, China Funding and conflicts of interest: Source of funding was not reported. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.	Inclusion criteria Patients aged ≥ 18 years who received tyrosine kinase inhibitor treatment for metastatic renal cell carcinoma. Exclusion criteria Patients treated with conventionally fractionated radiotherapy or received immunotherapy as first-line treatment. N total at baseline: Intervention: 85 Control: 105 Important prognostic factors[2]: *Median age (range)* *I: 55 (21–86)*	Stereotactic body radiation therapy plus tyrosine kinase inhibitor	Tyrosine kinase inhibitor	Length of follow-up: At least three months up to 10 years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Median overall survival I: 63.2 months C: 29.8 months P<0.001	Author's conclusion Combining SBRT with TKIs is tolerable and associated with longer OS in selected patients, such as those with oligometastasis and favorable or intermediate risk. Remarks - Retrospective design - SBRT delivered at various timepoints for different purposes - Cannot control for type and sequence of targeted regimens - Conducted at high-volume cancer center and results might be difficult to replicate in smaller centers.

		C: 54 (18–83) *Sex:* *I: 78.8% M* *C: 76.2% M* *Synchronous metastasis* *I: 41 (48.2)* *C: 56 (53.3)* Groups were comparable except that patients who received SBRT and TKI were older and more likely to have bone metastases.					
Russo, 2007	Type of study: Retrospective study Setting and country: Renal tumor database, Memorial Sloan Kettering Cancer Center, New York, US Funding and conflicts of interest: Not reported	Inclusion criteria: Patients who underwent a nephrectomy in the face of metastatic disease and patients who underwent a complete metastasectomy prior to, during, or subsequent to the nephrectomy. Exclusion criteria: Not reported. N total at baseline: Intervention: 61 Control: 30 Important prognostic factors[2]: Not reported Unclear if groups	Removal of the kidney and all metastatic sites (nephrectomy/complete metastasectomy)	Cytoreductive nephrectomy alone without resection of all metastatic sites	Length of follow-up: Median: 43 months I: 30 months C: 12 months Loss-to-follow-up: Not reported Incomplete outcome data: Missing data about preoperative laboratory values more frequent in complete metastasectomy group	Overall median survival I: 30 months C: 12 months	Author's conclusion This surgical experience provides a contemporary foundation as new targeted therapeutic agents are integrated into the neoadjuvant or adjuvant treatment of locally advanced and metastatic renal cancer. Remarks - Selection bias

		were comparable.					
Shin, 2020	Type of study: Retrospective study Setting and country: Korean Renal Cancer Study Group (University of Ulsan, Seoul National University, Sungkyunkwan University, National Cancer Center, Catholic University, Chonnam National University, and Korea University) Funding and conflicts of interest: Source of funding not reported. The authors declare that there are no conflict of interests.	Inclusion criteria: Patients who had PM-RCC at first mRCC diagnosis or at the initiation of first-line systemic therapy. Exclusion criteria: Patients with RCC involvement in the pancreas by disease progression following the first-line therapy and beyond. N total at baseline: *Synchronous PM-RCC* Intervention: 66 Control: C1: n=24 no surgery C2: n=14 only nephrectomy *Metachronous PM-RCC* Intervention: 132 Control: 64 Important prognostic factors[2]: Synchronous PM-RCC *Mean age ± SD* *I: 53.9 ± 14.2* *C1: 62.3 ± 9.7* *C2: 60.2 ±10.7* *Sex:* *I: 63.5% M* *C1: 75% M* *C2: 85.7% M*	Synchronous PM-RCC: Metastasectomy and nephrectomy Metachronous PM-RCC: Metastasectomy	Synchronous PM-RCC: - No surgery - Only nephrectomy Metachronous PM-RCC: No metastasectomy	Length of follow-up: Median follow-up of 25 months (IQR: 53.3 to 83.0) Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Overall survival *Synchronous PM-RCC* I: 23.7 months (12.2 to 59.3 months) C1: 16.8 months (8.8 to 25.1 months) C2: 18.1 months (9.3 to 69.5 months) P=0.121 *Metachronous PM-RCC* I: 53.7 months (25.3 to 83.4 months) C: 45.1 months (range: 20.4 to 67.8 months) P=0.012	Author's conclusion Compared to the other mRCC, PM-RCC demonstrated a favorable prognosis. Pancreas metastasectomy was associated with prolonged survival in the metachronous PM-RCC with a long progression-free period. Remarks: - Small number of participants

		Metachronous PM-RCC *Mean age ± SD* *I: 58.7 ± 11.1* *C: 65.3 ± 9.6* *Sex:* *I: 72.7% M* *C: 64.1% M* Groups not comparable					
Sun, 2018	Type of study: Retrospective study Setting and country: National Cancer Database, US Funding and conflicts of interest: Funded in part by the Trust family, Loker Pinard, and Michael Brigham Funds for Kidney Cancer Research (to T.K. Choueiri) at Dana-Farber Cancer Institute, the Dana-Farber/Harvard Cancer Center Kidney Cancer Program, and the Dana-Farber/Harvard Cancer Center Kidney Cancer SPORE P50	Inclusion criteria All patients >18 years old with a primary diagnosis of mRCC who underwent a cytoreductive nephrectomy Exclusion criteria Not reported N total at baseline: Intervention: 1695 Control: 1695 Important prognostic factors[2]: *Mean age (STE)* *I: 60.1 (0.232)* *C: 60.1 (0.244)* *Sex:* *I: 70.6% M* *C: 70.7% M* Groups were comparable	Metastasectomy	No metastasectomy	Length of follow-up: Up to 5 years Loss-to-follow-up: Patients that did not have follow-up data were excluded Incomplete outcome data: Not reported	Median overall survival I: 24.1 months C: 18.9 months	Author's conclusion MSX-treated patients may benefit from an improved overall survival compared to non-MSX treated patients. Good patient selection and a proper risk stratification strategy are still very important considerations. Remarks - Selection bias - Unclear which targeted therapy A total of 1976 patients underwent MSX (28.3%). Of those, 849 patients received targeted therapy (43.0%). Of note, 2581 (36.9%) received targeted therapy without MSX, whereas 2437 (34.8%) did not receive targeted therapy nor did they undergo MSX. Overall utilization rate of MSX increased significantly from 24.9% in 2006 to 31.4% in 2013 (EAPC: +2.18%, 95% CI: 0.35 to 4.04, p=0.03, Figure 1). In sub-analyses, we found that the increase was mainly driven by

	CA101942-01. None of the authors have any conflicts of interest to declare.						patients treated with MSX alone (EAPC: +3.78%, 95% CI: 1.00-6.64, p=0.015). Patients treated with MSX and targeted therapy did not observe a statistically significant increase over time (EAPC: 0.68%, 95% CI: -3.27-4.80, p=0.69).
Suzuki, 2022	Type of study: Retrospective study Setting and country: Kobe University Hospital in Japan Funding and conflicts of interest: The authors have not received any external funding for this study. The authors declare no conflicts of interest.	Inclusion criteria Patients with a history of nephrectomy for primary site of RCC who had been treated for solitary metastasis of RCC Exclusion criteria Not reported N total at baseline: Intervention: 29 Control: 44 Important prognostic factors[2]: *Median age (range)* *I: 68 (40–84)* *C: 68 (45–83)* *Sex:* *I: 75.9% M* *C: 81.8% M* Groups not comparable	Surgical metastasectomy	No surgical metastasectomy	Length of follow-up: Not reported Loss-to-follow-up: Not reported. Incomplete outcome data: Not reported.	Overall survival I: Not reached C: 62.9 months P=0.002 Perioperative complications I: None C: Not reported	Author's conclusion If resection is feasible, surgical metastasectomy may be beneficial for patients with solitary metastasis of RCC, and we showed the possibility that presurgical targeted therapy prior to surgical metastasectomy may be effective for avoiding recurrence after surgical metastasectomy. Remarks - Retrospective study with small number of patients → selection bias - Unevaluated confounders and missing data (e.g. tumor size and distance from vital organs)
Thomas, 2016	Type of study: Retrospective study Setting and country: The University of Texas	Inclusion criteria: Patients with RCC and sarcomatoid features with nephrectomy.	Metastasectomy	No metastasectomy	Length of follow-up: Not reported. Loss-to-follow-up: Censored on date of last contact	Overall survival *Synchronous sRCC* I: 8.4 months C: 8.0 months P=0.35	Author's conclusion In the current study, there was no clear evidence of benefit for patients with sRCC undergoing metastasectomy after

	MD Anderson Cancer Center, Houston, Texas, US <u>Funding and conflicts of interest:</u> The Biostatistics Resource Group is supported by the NIH/NCI under award number P30CA016672. Conflicts of interest not relevant to the current manuscript.	<u>Exclusion criteria</u>: Patients diagnosed with sRCC subsequent to nephrectomy (i.e., at time of metastasectomy) - No metastatic disease, with sarcomatoid percentage of 100%, in unreported clinical trials, with history of other metastatic malignancy, or with incomplete follow-up information <u>N total at baseline</u>: *Synchronous sRCC* Intervention: 30 Control: 26 *Asynchronous sRCC* Intervention: 10 Control: 14 <u>Important prognostic factors</u>[2]: Synchronous sRCC *Median age (IQR)* *I: 54 (47 to 64)* *C: 55 (49 to 63)* *Sex:* *I: 67% M* *C: 54% M* Asynchronous sRCC *Median age (IQR)* *I: 52 (48 to 60)* *C: 54 (49 to 58)*			<u>Incomplete outcome data</u>: Patients with unknown or missing values are not included in the comparison	*Asynchronous sRCC* I: 36.2 months C: 13.7 months P=0.29	nephrectomy. Particularly, the group of patients with pathological LN positive disease at nephrectomy has a considerably worse survival. <u>Remarks:</u> - Retrospective nature and long study time period, during which surgical and systemic treatment strategies have changed. - Small sample size

		Sex: *I: 70% M* *C: 36% M* Groups not comparable					
Tornberg, 2018	Type of study: Retrospective study Setting and country: Helsinki University Kidney Tumour Register Funding and conflicts of interest: This study was financially supported by the Competitive State Research Financing of the Expert Responsibility area of Helsinki University Hospital. No conflicts of interest to declare or no relevant conflict of interest (outside submitted work)	Inclusion criteria: - Patients with sporadic mRCC treated by surgery for adrenal or lymph node metastases - Primary tumor was inevitably treated by surgery - Patients treated by either radical or cytoreductive intention in the initial operation, nephrectomy or nephrectomy combined with simultaneous metastasectomy for RCC Exclusion criteria: - Patients who received palliative treatment alone for metastases - Patients with coincidentally encountered lymph node involvement or minimal findings in the adrenal gland. N total at baseline: Intervention: 46 Control: 51	Complete metastasectomy	Non-complete metastasectomy	Length of follow-up: 12 years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	5-year overall survival I: 59% C: 45% P=0.002 Interval time from diagnosis to oncological treatment I: not achieved C: 19 months (1-71 months)	Author's conclusion Metastasectomy is an option for selected patients with mRCC. Complete resection should be attempted when feasible. Remarks: - Number of patients with metastases fit for surgery remained low

		Important prognostic factors[2]: Not reported Unclear if groups were comparable.					
You, 2016	Type of study: Retrospective study Setting and country: Asan Medical Center, Korea Funding and conflicts of interest: Source of funding not reported. All authors declare that they have no conflict of interest.	Inclusion criteria: Patients presented with mRCC but without prior systemic therapy Exclusion criteria: Patients who underwent consolidation metastasectomy after targeted therapy N total at baseline: Intervention: 33 Control: C1 incomplete: 29 C2 no: 263 Important prognostic factors[2]: *Mean age (SD)* *I: 56.1 (8.9)* *C1: 53.6 (10.3)* *C2: 59.3 (12.1)* *Sex* *I: 75.8% M* *C1: 55.2% M* *C2: 71.1% M* *Synchronous metastases* *I: 5 (15.2%)* *C1: 15 (51.7%)* *C2: 160 (60.8%)*	Complete metastasectomy followed by targeted therapy	Incomplete metastasectomy followed by targeted therapy Non-metastasectomy (only targeted therapy)	Length of follow-up: Up to 16 months Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Overall survival I: 92.5 months C1: 29.6 months C2: 23.5 months	Author's conclusion Complete metastasectomy performed before targeted therapy might improve progression-free and overall survivals in patients with mRCC. Remarks - Retrospective nature: confounding variables - Small number of participants

		Groups not comparable.					
Yu, 2015	Type of study: Retrospective study Setting and country: Peking University First Hospital, China Funding and conflicts of interest: Source of funding not reported. The authors declare that there is no conflict of interests regarding the publication of this paper.	Inclusion criteria - Patients diagnosed with metastatic renal cell carcinoma - Oligometastasis - Karnofsky Performance Scale not less than 80 Exclusion criteria - No previous nephrectomy - Incomplete data concerning survival time, pathology, metastatic sites, and detailed record of surgery N total at baseline: Intervention: 31 Control: C1 incomplete: 11 C2 no: 54 Important prognostic factors[2]: *Sex* *I: 90.3% M* *C1: 81.8% M* *C2: 75.9% M* *Age (65 or more)* *I: 29%* *C1: 27%* *C2: 26%* Groups not comparable.	Complete metastasectomy	Incomplete metastasectomy No metastasectomy	Length of follow-up: Median of 45 months (range 2 to 112 months) Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Overall survival I: 52 months (95% CI: 26.8–77.2) C1: 16 months (95% CI: 9.5–22.5) C2: 22 months (95% CI: 17.6–26.4) P=0.001	Author's conclusion In the era of targeted therapy, complete metastasectomy can improve overall survival. Complete metastasectomy, T stage > 3, disease free interval <12 months, and multiorgan involvement are independent prognostic factors. Remarks - Bias due to retrospective design - Small number of participants - Incomplete records on specific targeted therapy usage

Risk of bias table for interventions studies (cohort studies based on risk of bias tool by the CLARITY Group at McMaster University)

Author, year	Selection of participants Was selection of exposed and non-exposed cohorts drawn from the same population?	Exposure Can we be confident in the assessment of exposure?	Outcome of interest Can we be confident that the outcome of interest was not present at start of study?	Confounding-assessment Can we be confident in the assessment of confounding factors?	Confounding-analysis Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?	Assessment of outcome Can we be confident in the assessment of outcome?	Follow up Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?	Co-interventions Were co-interventions similar between groups?	Overall Risk of bias
Alt, 2011	Probably yes Reason: Participants were selected from same hospital.	Probably yes Reason: Probably derived from medical records.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of patients were provided.	Probably yes Reason: Multivariate analysis was performed.	Probably yes Reason: Probably derived from death certificates.	Probably yes Reason: No missing data.	Probably no Reason: The use of systemic therapy differed between both groups.	**Some concerns**
Dragomir, 2020	Definitely yes Reason: Participants were selected	Definitely yes Reason: Derived from patient's	Definitely yes Reason: Outcome of interest could not be present	Definitely yes Reason: Obtained by patient survey and	Probably yes Reason: Exposed and unexposed were matched on specific variables.	Probably yes Reason: Derived from database.	Probably yes Reason: No missing data.	Probably yes Reason: Targeted therapy was	**Low**

	from the same database.	medical records.	at the start (survival).	medical record review.				balanced between groups	
Fares, 2019	Probably yes Reason: Participants were selected from the same biobank.	Probably yes Reason: Derived from biobank.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided by electronic medical chart.	Probably yes Reason: Exposed and unexposed are matched and balanced.	Probably yes Reason: Derived from biobank.	Probably yes Reason: No missing data.	Probably no Reason: Systemic treatment was different in both groups.	**Some concerns**
Ishihara, 2020	Probably yes Reason: Participants were selected from the same institution.	Probably yes Reason: Derived from electronic database and patient medical records.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided by electronic database and patient medical records.	Probably yes Reason: Multivariable analysis was performed.	Probably yes Reason: Derived from electronic database and patient medical records.	Probably no Reason: Follow-up was relatively short.	Probably no Reason: Systemic treatment was different in both groups.	**Some concerns**
Kim, 2019	Probably yes Reason: Participants were selected from the same registry database.	Probably yes Reason: Derived from registry database.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided by medical records.	Probably yes Reason: Multivariable analysis was performed.	Probably yes Reason: Derived from medical records	Probably yes Reason: No missing data.	Probably no Reason: Cytoreductive nephrectomy, readiation therapy and embolization different	**Some concerns**

								between groups.	
Kwak, 2007	Probably yes Reason: Participants selected from medical records.	Probably yes Reason: Derived from patient's medical records.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided.	Probably yes Reason: Multivariate analysis was performed.	Probably yes Reason: Derived from patient's medical record.	Probably yes Reason: No missing data.	Probably yes Reason: No other interventions provided.	**Low**
Li, 2018	Probably yes Reason: Participants selected from same hospital.	Probably yes Reason: Derived from chart-review.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided.	Probably yes Reason: Multivariate analysis was performed.	Probably yes Reason: Derived from chart-review.	Probably yes Reason: Patients with incomplete data were excluded.	Probably no Reason: Targeted therapy was not identical.	**Some concerns**
Liu, 2018	Probably yes Reason: Participants selected from same center.	Probably yes Reason: Derived from medical records.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided.	Probably yes Reason: Multivariate analysis was performed.	Probably yes Reason: Derived from chart-review.	Probably yes Reason: No missing data.	Probably yes Reason: Other intervention (nephrectomy) similar between groups.	**Low**
Russo, 2007	Probably yes	Probably yes	Definitely yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	**Some concerns**

	Reason: Participants selected from same database.	Reason: Database was queried to identify exposed patients.	Reason: Outcome of interest could not be present at the start (survival).	Reason: Characteristics of participants were provided.	Reason: No adjustment for confounders.	Reason: Derived from database.	Reason: No missing data for outcome of interest.	Reason: No other interventions provided.	
Shin, 2020	Definitely yes Reason: Participants were selected from the same database.	Probably yes Reason: Derived from database.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided.	Probably yes Reason: Multivarate analysis was performed.	Probably yes Reason: Derived from database.	Probably yes Reason: No missing data.	No information Unclear how targeted therapy was administered in both groups	**Some concers**
Sun, 2018	Probably yes Reason: Participants were selected from the same database.	Probably yes Reason: Derived from database.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided.	Probably yes Reason: Exposed and unexposed were matched.	Probably yes Reason: Derived from database.	Probably yes Reason: No missing data.	No information Unclear how targeted therapy was administered in both groups	**Some concerns**
Suzuki, 2022	Probably yes Reason: Participants were selected from the same hospital.	Probably yes Reason: Derived from medical records.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided from medical records.	Probably no Reason: Some multivariate analyses were performed, but also unevaluated confounders.	Probably yes Reason: Derived from medical records.	Probably yes Reason: No missing data.	No information Unclear if non-metastasectomy group also received systemic therapy.	**High**

Thomas, 2016	Probably yes Reason: Participants were selected from the same database.	Probably yes Reason: Derived from database.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided.	Probably yes Reason: Exposed and unexposed are matched.	Probably yes Reason: Derived from database.	Probably yes Reason: Missing values not included in the comparison.	Probably no Reason: Systemic therapy different between groups	**Some concerns**
Tornberg, 2018	Definitely yes Reason: Participants were selected from the same register.	Probably yes Reason: Derived from register.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably no Reason: No characteristics presented for patients with complete/non-complete metastasectomy.	Probably yes Reason: Multivarate analysis was performed.	Probably yes Reason: Derived from patient registry.	Probably yes Reason: No missing data.	No information No data presented for complete/non-complete metastasectomy	**Some concerns**
You, 2016	Probably yes Reason: Participants were selected from the same medical center.	Probably yes Reason: Derived from medical records.	Definitely yes Reason: Outcome of interest could not be present at the start (survival).	Probably yes Reason: Characteristics of participants were provided.	Probably yes Reason: Multivariate analysis was performed.	Probably yes Reason: Derived from medical records.	Probably yes Reason: No missing data.	Probably yes Reason: No other interventions.	**Low**
Yu, 2015	Probably yes	Probably yes	Definitely yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably no	**Some concerns**

	Reason: Participants were selected from the same hospital.	Reason: Probably derived from medical records.	Reason: Outcome of interest could not be present at the start (survival).	Reason: Characteristics of participants were provided.	Reason: Multivariate analysis was performed.	Reason: Derived from medical records.	Reason: No missing data.	Reason: Unclear which targeted therapy was administered.	

Table of excluded studies

Reference	Reason for exclusion
Alt AL, Boorjian SA, Lohse CM, Costello BA, Leibovich BC, Blute ML. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. Cancer. 2011 Jul 1;117(13):2873-82. doi: 10.1002/cncr.25836. Epub 2011 Jan 10. PMID: 21692048	Included in systematic review of Hsieh 2021
Dabestani S, Marconi L, Hofmann F, Stewart F, Lam TB, Canfield SE, Staehler M, Powles T, Ljungberg B, Bex A. Local treatments for metastases of renal cell carcinoma: a systematic review. Lancet Oncol. 2014 Nov;15(12):e549-61. doi: 10.1016/S1470-2045(14)70235-9. Epub 2014 Oct 26. PMID: 25439697.	More recent systematic review with overlap in included studies available
Haque W, Verma V, Butler EB, Teh BS. Utilization of Stereotactic Radiosurgery for Renal Cell Carcinoma Brain Metastases. Clin Genitourin Cancer. 2018 Aug;16(4):e935-e943. doi: 10.1016/j.clgc.2018.03.015. Epub 2018 Apr 3. PMID: 29680768.	Wrong comparison: stereotactic radiosurgery versus whole brain radiation therapy
Ishihara H, Takagi T, Kondo T, Fukuda H, Tachibana H, Yoshida K, Iizuka J, Kobayashi H, Ishida H, Tanabe K. Prognostic impact of metastasectomy in renal cell carcinoma in the postcytokine therapy era. Urol Oncol. 2021 Jan;39(1):77.e17-77.e25. doi: 10.1016/j.urolonc.2020.08.011. Epub 2020 Aug 28. PMID: 32863124.	Included in systematic review of Hsieh 2021
Kwak C, Park YH, Jeong CW, Lee SE, Ku JH. Metastasectomy without systemic therapy in metastatic renal cell carcinoma: comparison with conservative treatment. Urol Int. 2007;79(2):145-51. doi: 10.1159/000106329. PMID: 17851285.	Included in systematic review of Hsieh 2021
Kim DY, Karam JA, Wood CG. Role of metastasectomy for metastatic renal cell carcinoma in the era of targeted therapy. World J Urol. 2014 Jun;32(3):631-42. doi: 10.1007/s00345-014-1293-6. Epub 2014 Apr 18. PMID: 24744223.	Wrong study design: narrative review
Li JR, Ou YC, Yang CK, Wang SS, Chen CS, Ho HC, Cheng CL, Yang CR, Chen CC, Wang SC, Lin CY, Hung SC, Hsu CY, Chiu KY. The Impact of Local Intervention Combined with Targeted Therapy on Metastatic Renal Cell Carcinoma. Anticancer Res. 2018 Sep;38(9):5339-5345. doi: 10.21873/anticanres.12861. PMID: 30194186.	Included in systematic review of Hsieh 2021
Liu Y, Long W, Zhang Z, Zhang Z, Mai L, Huang S, Han H, Zhou F, Dong P, He L. Metastasis-directed stereotactic body radiotherapy for oligometastatic renal cell carcinoma: extent of tumor burden eradicated by radiotherapy. World J Urol. 2021 Nov;39(11):4183-4190. doi: 10.1007/s00345-021-03742-1. Epub 2021 May 27. PMID: 34043023; PMCID: PMC8571216.	Wrong intervention: among the patients receiving SBRT, systemic therapies were initiated after SBRT in 5 patients. The remaining patients started systemic therapy before SBRT. Some patients in both groups also received metastasectomy.

Lyon TD, Thompson RH, Shah PH, Lohse CM, Boorjian SA, Costello BA, Cheville JC, Leibovich BC. Complete Surgical Metastasectomy of Renal Cell Carcinoma in the Post-Cytokine Era. J Urol. 2020 Feb;203(2):275-282. doi: 10.1097/JU.0000000000000488. Epub 2019 Aug 8. PMID: 31393812.	Wrong comparison: also, nonsurgical therapy
Masini C, Iotti C, De Giorgi U, Bellia RS, Buti S, Salaroli F, Zampiva I, Mazzarotto R, Mucciarini C, Vitale MG, Bruni A, Lohr F, Procopio G, Caffo O, Nole F, Morelli F, Baier S, Buttigliero C, Ciammella P, Timon G, Fantinel E, Carlinfante G, Berselli A, Pinto C. Nivolumab in Combination with Stereotactic Body Radiotherapy in Pretreated Patients with Metastatic Renal Cell Carcinoma. Results of the Phase II NIVES Study. Eur Urol. 2022 Mar;81(3):274-282. doi: 10.1016/j.eururo.2021.09.016. Epub 2021 Oct 1. PMID: 34602312.	Wrong population: second- and third-line mRCC patients
Onal C, Hurmuz P, Guler OC, Yavas G, Tilki B, Oymak E, Yavas C, Ozyigit G. The role of stereotactic body radiotherapy in switching systemic therapy for patients with extracranial oligometastatic renal cell carcinoma. Clin Transl Oncol. 2022 Aug;24(8):1533-1541. doi: 10.1007/s12094-022-02793-z. Epub 2022 Feb 4. PMID: 35119653.	No comparison: only SBRT
Ouzaid I, Capitanio U, Staehler M, Wood CG, Leibovich BC, Ljungberg B, Van Poppel H, Bensalah K; Young Academic Urologists Kidney Cancer Working Group of the European Association of Urology. Surgical Metastasectomy in Renal Cell Carcinoma: A Systematic Review. Eur Urol Oncol. 2019 Mar;2(2):141-149. doi: 10.1016/j.euo.2018.08.028. Epub 2018 Sep 24. PMID: 31017089.	Included studies were retrospective and non-comparative
Staehler MD, Kruse J, Haseke N, Stadler T, Roosen A, Karl A, Stief CG, Jauch KW, Bruns CJ. Liver resection for metastatic disease prolongs survival in renal cell carcinoma: 12-year results from a retrospective comparative analysis. World J Urol. 2010 Aug;28(4):543-7. doi: 10.1007/s00345-010-0560-4. Epub 2010 May 4. PMID: 20440505.	Included in systematic review of Hsieh 2021, but wrong comparison (partial resection versus no surgery; control group refused surgery)
Sun M, Meyer CP, Karam JA, de Velasco G, Chang SL, Pal SK, Trinh QD, Choueiri TK. Predictors, utilization patterns, and overall survival of patients undergoing metastasectomy for metastatic renal cell carcinoma in the era of targeted therapy. Eur J Surg Oncol. 2018 Sep;44(9):1439-1445. doi: 10.1016/j.ejso.2018.05.026. Epub 2018 Jun 5. PMID: 29935840.	Included in systematic review of Hsieh 2021
Verbiest A, De Meerleer G, Albersen M, Beuselinck B. Non-Surgical Ablative Treatment of Distant Extracranial Metastases for Renal Cell Carcinoma: A Systematic Review. Kidney Cancer 2018; 2(1), 57-67.	C does not match PICO
Verbiest A, Roussel E, Tosco L, Joniau S, Laenen A, Clement P, Beuselinck B. Long-term outcomes in clear-cell renal cell carcinoma patients treated with complete metastasectomy. Kidney Cancer 2020; 4(4), 177-183.	Wrong comparison: systemic therapy

You D, Lee C, Jeong IG, Song C, Lee JL, Hong B, Hong JH, Ahn H, Kim CS. Impact of metastasectomy on prognosis in patients treated with targeted therapy for metastatic renal cell carcinoma. J Cancer Res Clin Oncol. 2016 Nov;142(11):2331-8. doi: 10.1007/s00432-016-2217-1. Epub 2016 Aug 23. PMID: 27553579	Included in systematic review of Hsieh 2021
Yu X, Wang B, Li X, Lin G, Zhang C, Yang Y, Fang D, Song Y, He Z, Zhou L. The Significance of Metastasectomy in Patients with Metastatic Renal Cell Carcinoma in the Era of Targeted Therapy. Biomed Res Int. 2015;2015:176373. doi: 10.1155/2015/176373. Epub 2015 Oct 11. PMID: 26568955; PMCID: PMC4619757.	Included in systematic review of Hsieh 2021
Zaid HB, Parker WP, Safdar NS, Gershman B, Erwin PJ, Murad MH, Boorjian SA, Costello BA, Thompson RH, Leibovich BC. Outcomes Following Complete Surgical Metastasectomy for Patients with Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. J Urol. 2017 Jan;197(1):44-49. doi: 10.1016/j.juro.2016.07.079. Epub 2016 Jul 26. PMID: 27473875.	More recent systematic review with overlap in included studies available

Literature search strategy

Richtlijn: Herziening Niercelcarcinoom	
Uitgangsvraag: Welke behandeling (chirurgische metastasectomie, SBRT, ablatie) kan het beste worden toegepast bij patiënten met a) synchrone oligometastasen / b) metachrone oligometastasen?	
Database(s): Medline (OVID), Embase	Datum: 12-04-2022
Periode: >2000	Talen: Engels, Nederlands
Literatuurspecialist: Linda Niesink	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: → Voor deze vraag is gezocht op de elementen **(oligo)metastasen** (in het groen), **niercelcarcinoom** (in het blauw), en **metastasectomie, radiotherapie en/of ablatie** (in het oranje). → Resultaten staan in Rayyan.	
Te gebruiken voor richtlijnen tekst: In de databases Embase (via embase.com) en Medline (via OVID) is op 12-04-2022 met relevante zoektermen gezocht naar systematische reviews, RCT's en observationele studiedesigns over metastasectomie, radiotherapie en/of ablatie bij patiënten met synchrone of metachrone (oligo)metastasen bij niercelcarcinoom. De literatuurzoekactie leverde 1094 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**

SRs	114	91	143
RCTs	222	71	253
	510	501	698
Totaal	846	663	**1094**

Zoekstrategie

Database	**Zoektermen**		
Embase	*No.*	*Query*	*Results*
	#1	'renal cell carcinoma'/exp OR 'non clear cell renal cell carcinoma'/exp OR (('kidney cell*' OR 'renal cell*' OR nephroid OR hypernephroid OR 'collecting duct') NEAR/3 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR mass*)):ti,ab,kw) OR ((grawitz* NEAR/3 (tumor* OR tumour*)):ti,ab,kw) OR hypernephroma*:ti,ab,kw OR 'hyper nephroma*':ti,ab,kw OR rcc:ti,kw OR mrcc:ti,kw OR nccrcc:ti,ab,kw OR ncrcc:ti,ab,kw	82144
	#2	'oligometastasis'/exp OR oligometasta*:ti,ab,kw OR 'multiple tumor'/exp OR 'second primary neoplasm'/exp OR synchron*:ti,ab,kw OR metachron*:ti,ab,kw OR 'metastasis'/exp/mj OR metasta*:ti,ab,kw OR advanced:ti,ab,kw OR mrcc:ti,ab,kw	1686463
	#3	'ablation therapy'/exp OR 'tumor ablation'/exp OR 'metastasis resection'/exp OR 'radiofrequency ablation'/exp OR 'microwave thermotherapy'/exp OR 'percutaneous ablation'/exp OR 'stereotactic body radiation therapy'/exp OR ablation:ti,ab,kw OR metastasectom*:ti,ab,kw OR metastectom*:ti,ab,kw OR ((metastasis NEAR/3 (resect* OR excision)):ti,ab,kw) OR 'radiofrequency ablation':ti,ab,kw OR ((microwave NEAR/3 (ablation OR therap* OR thermotherap*)):ti,ab,kw) OR ((stereotactic NEAR/3 (radiation OR radiotherap* OR radiosurger* OR therap*)):ti,ab,kw)	224479
	#4	#1 AND #2 AND #3 AND ([english]/lim OR [dutch]/lim) AND [2000-2022]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	1521
	#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature')	786647

		NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
	#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3444120
	#7	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR	12774067

	control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab))) #8 #4 AND #5 **– SR's** 114 #9 #4 AND #6 NOT #8 **– RCT's** 222 #10 #4 AND #7 NOT (#8 OR #9) **– observationele studies** 510 #11 #8 OR #9 OR #10 846
Medline (OVID)	1 exp Carcinoma, Renal Cell/ or exp Kidney Neoplasms/ or (('kidney' or 'renal' or nephroid or hypernephroid or 'collecting duct') adj3 (cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or mass*)).ti,ab,kf. or (grawitz* adj3 (tumor* or tumour*)).ti,ab,kf. or hypernephroma*.ti,ab,kf. or (RCC or MRCC or nccrcc or ncrcc).ti,ab,kf. (113711) 2 exp Neoplasm Metastasis/ or (advanced or metasta* or oligometasta* or synchron* or metachron* or mrcc).ti,ab,kf. (1186195) 3 exp Metastasectomy/ or exp Radiofrequency Ablation/ or exp Radiotherapy/ or (ablation or metastasectom* or metastectom*).ti,ab,kf. or (metastasis adj3 (resect* or excision*)).ti,ab,kf. or (microwave adj3 (ablation or therap* or thermotherap*)).ti,ab,kf. or (stereotactic adj3 (radiation or radiotherap* or radiosurger* or therap*)).ti,ab,kf. (325116) 4 1 and 2 and 3 (2243) 5 limit 4 to ((english or dutch) and yr="2000 -Current") (1713) 6 5 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (1643) 7 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or

	"structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) (585374) 8 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (1366536) 9 Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) (5129254) 10 6 and 7 (91) **– SRs** 11 (6 and 8) not 10 (71) **- RCTs** 12 (6 and 9) not (10 or 11) (501) **– observationele studies** 13 10 or 11 or 12 (663)

Bijlagen bij module 5

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Overweeg een cytoreductieve nefrectomie bij patiënten met een aanhoudende periode van een complete of bijna complete response van de metastasen om een ziektevrije situatie (no evidence of disease NED) te bereiken.	1-3 jaar	Onduidelijk, maar waarschijnlijk kostenbesparing omdat therapie-vrije interval 2,5 jaar is	Beschikbaarheid systeemtherapie Kennis van richtlijnmodule	Gebrek aan kennis van richtlijnmodule	Dissemina tie module	NVU NIV (NVMO)	
Overweeg een cytoreductieve nefrectomie na immuuntherapie bij patiënten bij wie de primaire tumor groeit ondanks controle van de afstandsmetastasen.	1-3 jaar	Onduidelijk, maar waarschijnlijk kostenbesparing omdat therapie-vrije interval 2,5 jaar is	Beschikbaarheid systeemtherapie Kennis van richtlijnmodule	Gebrek aan kennis van richtlijnmodule	Dissemina tie module	NVU NIV (NVMO)	

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel,

nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Evidence tables

Research question: What is the place of cytoreductive therapy in addition to systemic immunotherapy in patients with metastasized renal cell carcinoma?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
1st author, year of publication Singla, 2021	Type of study: Cohort study Setting and country: USA Funding and conflicts of interest: 1. Ruth L. Kirschstein National Research Service Award 2. The University of Texas Southwestern Medical Center Physician Scientist Training Program 3. Dedman Family Scholarship in Clinical Care	<u>Inclusion criteria</u>: - Renal cancer cases from 2015 and later (2015 and 2016) - Metastatic at diagnosis - Patients receiving immunotherapy <u>Exclusion criteria</u>: - Renal cancer cases preceding 2015 - Patients receiving any non immuno systemic therapy - Patients with Charlson-Deyo comorbidity score >2 <u>N total at baseline</u>: 391 Intervention: 221 Control: 170	Describe intervention (treatment/procedure/test): CN + immunotherapy (IO)	Describe control (treatment/procedure/test): IO alone	<u>Length of follow-up</u>: *Patient information retrieved from the National Cancer Database (USA) for the cohort between in 2015 and 2016.* Follow-up ranged from 2 to 34 months <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): ***The uni- and multivariable analysis was conducted with patients diagnosed in 2015 only (N= 185)*** <u>Outcome measure-1:</u> **Progression-free survival rate** Not reported. <u>Outcome measure-2:</u> **Overall survival rate** Median OS (months) *Univariable analysis*: *I:* median OS not reached *C:* 11.6, 95% CI (8.5 to 14.7) HR 0.23, 95% CI (0.15 to 0.37) p < 0.001 in favour of CN + IO *Multivariable Cox regression analyses (defined a priori)**: HR 0.22, 95% CI (0.11 to 0.42) p < 0.001 in favour of CN +IO	The authors conclude: *Patients who received CN+IO exhibited significantly better OS than those who received IO alone. Using multiple multivariable models, receipt of CN remained the strongest and only independent predictor for OS.* Available information on statistical analysis: *OS was compared between the two cohorts using Kaplan-Meier methods, and differences were analyzed with the log-rank statistic. Clinicopathologic predictors for OS were assessed using multivariable Cox regression analyses. Multivariable analyses incorporated models involving a priori selection of clinically-relevant covariates and contingent selection of covariates based on*

	The authors report no conflicts of interest.	<u>Important prognostic factors</u>[2]: *age median years (IQR)* *I:* 57 (51 to 64) *C:* 64 (57 to 72) *Sex:* *I:* 75.6 % M *C:* 70.6 % M *Primary tumor size Median (IQR) cm:* *I:* 9.7 (7.4 to 12.0) *C:* 8.0 (5.8 to 11.0) *Presence of liver metastases (%):* *I:* Yes: 7.7 No: 86.9 Unknown: 5.4 *C:* Yes: 20.0 No: 67.6 Unknown: 12.4 Groups comparable at baseline? Differences between groups are described above. Otherwise, baseline				*Adjusted for adjusted for age, locally advanced cT stage, cN1 stage and the presence of bone, liver or brain metastases. <u>Outcome measure-3:</u> **Quality of life** Not reported. <u>Outcome measure-4:</u> **Complications** Not reported.	*significance in univariable analysis.*

		demographics and Charlson-Deyo comorbidity score were similar between groups. The frequency of brain, bone, and pulmonary metastases was comparable between groups, with no significant difference in the number of known metastatic sites. Sarcomatoid features were present in 22 patients (5.6%) and similarly distributed between groups.					

Risk of bias table for interventions studies (cohort studies based on risk of bias tool by the CLARITY Group at McMaster University)

Author, year	Selection of participants Was selection of exposed and non-exposed cohorts drawn from the same population?	Exposure Can we be confident in the assessment of exposure?	Outcome of interest Can we be confident that the outcome of interest was not present at start of study?	Confounding-assessment Can we be confident in the assessment of confounding factors?	Confounding-analysis Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?	Assessment of outcome Can we be confident in the assessment of outcome?	Follow up Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?	Co-interventions Were co-interventions similar between groups?	Overall Risk of bias
Singla, 2021	Definitely yes Reason: Participants were selected from a registry in the same time frame	Probably yes Reason: Data from American National Cancer Database	Definitely yes Reason: Outcome is overall survival.	Probably yes Reason: Data extracted from database, unlcear if all confounding variables of interest were accounted for	Probably yes Reason: Variables were taken into account in the multivariate analysis.	Probably yes Reason: Obtained from American National Cancer Database	**Definetely no** Reason: Follow-up was highly variable, reasons not reported. Only data for a subgroup of the full sample reported	No information	**Some concerns (Progression free survival, overall survival)**

Table of excluded studies

Reference	Reason for exclusion
Alnimer, Y., Qasrawi, A., Yan, D., & Wang, P. (2021). Prognostic Impact of Cytoreductive Nephrectomy in Patients with Metastatic Renal Cell Carcinoma: Data from a Large Population-Based Database. *Urology Journal*, *19*(02), 111-119.	Wrong C
Bamias, A., Escudier, B., Sternberg, C. N., Zagouri, F., Dellis, A., Djavan, B., ... & Constantinides, C. A. (2017). Current clinical practice guidelines for the treatment of renal cell carcinoma: a systematic review and critical evaluation. *The oncologist*, *22*(6), 667-679.	Review of guidelines
Bell, H., Cotta, B. H., Salami, S. S., Kim, H., & Vaishampayan, U. (2022). "PROBE" ing the Role of Cytoreductive Nephrectomy in Advanced Renal Cancer. *Kidney Cancer*, *6*(1), 3-9.	Wrong study design, protocol paper
Dawsey, S. J., Campbell, S. C., & Ornstein, M. C. (2021). Cytoreductive nephrectomy following immunotherapy-base treatment in metastatic renal cell carcinoma: a case series and review of current literature. *Current Oncology*, *28*(3), 1921-1926.	Wrong study design, case series
Dilme, R. V., Rivas, J. G., Campi, R., Puente, J., Jerez, T., Enikeev, D., ... & Sierra, J. M. (2021). Cytoreductive Nephrectomy in the Management of Metastatic Renal Cell Carcinoma: Is There Still a Debate?. *Current Urology Reports*, *22*, 1-11.	Wrong study design, narrative review
Dragomir, A., Nazha, S., Tanguay, S., Breau, R. H., Bhindi, B., Rendon, R. A., ... & Wood, L. A. (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.	Wrong I
Ghatalia, P., Handorf, E. A., Geynisman, D. M., Deng, M., Zibelman, M. R., Abbosh, P., ... & Uzzo, R. G. (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.	Wrong I
Gulati, S., & Vaishampayan, U. (2020). Current state of systemic therapies for advanced renal cell carcinoma. *Current Oncology Reports*, *22*, 1-10.	Wrong atudy design, narrative review
Gulati, S., & Vaishampayan, U. (2020). Current state of systemic therapies for advanced renal cell carcinoma. *Current Oncology Reports*, *22*, 1-10.	Wrong atudy design, narrative review
Hall, M. E., Bhindi, B., Luckenbaugh, A. N., Laviana, A. A., Moses, K. A., Satkunasivam, R., ... & Wallis, C. J. (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*, *32*(7), 675-680.	Wrong comparison, IO or TT combined with CN
Hishida, T., Masai, K., Kaseda, K., Asakura, K., & Asamura, H. (2021). Debulking surgery for malignant tumors: the current status, evidence and future perspectives. *Japanese journal of clinical oncology*, *51*(9), 1349-1362.	Wrong atudy design, narrative review
Hsiang, W. R., Kenney, P. A., & Leapman, M. S. (2020). Redefining the role of surgical management of metastatic renal cell carcinoma. *Current Oncology Reports*, *22*, 1-9.	Wrong atudy design, narrative review

Ishihara, H., Takagi, T., Kondo, T., Fukuda, H., Tachibana, H., Yoshida, K., ... & Tanabe, K. (2021). Prognostic impact of systemic therapy change in metastatic renal cell carcinoma treated with cytoreductive nephrectomy. *Japanese Journal of Clinical Oncology*, *51*(2), 296-304.	Wrong comparison. No analysis of IO vs. IO+CN
Kato, R., Naito, S., Numakura, K., Hatakeyama, S., Koguchi, T., Kojima, T., ... & Obara, W. (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.	Wrong comparison, systemic thearpy + CN compared to systemic theray + no CN or deffered CN
Kikuchi, H., Osawa, T., Matsumoto, R., Abe, T., Maruyama, S., Harabayashi, T., ... & Shinohara, N. (2022, January). Efficacy of nivolumab plus ipilimumab as first-line therapy for primary tumors in patients with renal cell carcinoma. In *Urologic Oncology: Seminars and Original Investigations* (Vol. 40, No. 1, pp. 13-e19). Elsevier.	Wrong comparison. No analysis of IO vs. IO+CN
Kim, S. H., Kim, J. K., Park, B., Joo, J., Joung, J. Y., Seo, H. K., ... & Chung, J. (2017). Effect of renal embolization in patients with synchronous metastatic renal cell carcinoma: A retrospective comparison of cytoreductive nephrectomy and systemic medical therapy. *Oncotarget*, *8*(30), 49615.	Wrong comparison, renal embolization compared to CN and no primary renal treatment
Kuusk, T., Szabados, B., Liu, W. K., Powles, T., & Bex, A. (2019). Cytoreductive nephrectomy in the current treatment algorithm. *Therapeutic advances in medical oncology*, *11*, 1758835919879026.	Wrong atudy design, narrative review
Ljungberg, B., Sundqvist, P., Lindblad, P., Kjellman, A., Thorstenson, A., Hellström, M., ... & Lundstam, S. (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.	Wrong I
Mazzaschi, G., Quaini, F., Bersanelli, M., & Buti, S. (2021). Cytoreductive nephrectomy in the era of targeted-and immuno-therapy for metastatic renal cell carcinoma: an elusive issue? A systematic review of the literature. *Critical Reviews in Oncology/Hematology*, *160*, 103293.	Wrong O
Meerveld-Eggink, A., Graafland, N., Wilgenhof, S., Van Thienen, J. V., Lalezari, F., Grant, M., ... & Bex, A. (2022). Primary renal tumour response in patients treated with nivolumab and ipilimumab for metastatic renal cell carcinoma: real-world data assessment. *European Urology Open Science*, *35*, 54-58.	Wrong O
Mori, K., Quhal, F., Yanagisawa, T., Katayama, S., Pradere, B., Laukhtina, E., ... & Shariat, S. F. (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.	Wrong comparison, combination therapy vs sunitinib with and without CN
Patel, H. V., Shinder, B., Srinivasan, R., & Singer, E. A. (2020). Challenges and opportunities in the management of metastatic renal cell carcinoma: combination therapy and the role of cytoreductive surgery. *Current opinion in oncology*, *32*(3), 240-249.	Wrong atudy design, narrative review
Rappold, P. M., Silagy, A. W., Kotecha, R. R., & Hakimi, A. A. (2021). Immune checkpoint blockade in renal cell carcinoma. *Journal of surgical oncology*, *123*(3), 739-750.	Wrong atudy design, narrative review

Shapiro, D. D., Westerman, M. E., Karam, J. A., & Wood, C. G. (2020). Cytoreductive Nephrectomy in Patients Presenting With Advanced Disease: Have We Finally Answered the Question?. *The Cancer Journal*, *26*(5), 382-389.	Wrong atudy design, narrative review
Stellato, M., Santini, D., Verzoni, E., De Giorgi, U., Pantano, F., Casadei, C., ... & Procopio, G. (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.	Wrong P
Tabakin, A. L., Stein, M. N., Anderson, C. B., Drake, C. G., & Singer, E. A. (2020). Cytoreductive nephrectomy for metastatic renal cell carcinoma, the ultimate urologic 'Choosing Wisely'campaign: a narrative review. *Translational cancer research*, *9*(11), 7337.	Wrong atudy design, narrative review
Teishima, J., Goto, K., Sekino, Y., Mita, K., Hayashi, T., Hasegawa, Y., ... & Hinata, N. (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.	Wrong atudy design, prognostic study
Zhang, Y., Hu, J., Yang, J., Xie, Y., Chen, Z., Shangguan, W., ... & Xie, W. (2022). Selection of optimal candidates for cytoreductive nephrectomy in patients with metastatic clear cell renal cell carcinoma: a predictive model based on SEER database. *Frontiers in Oncology*, *12*, 24.	Wrong study design, predictive model

Literature search strategy

Search date: 31-03-2022
Hits: 281

Database	Zoektermen		
Embase	*No.*	*Query*	*Results*
	#1	'renal cell carcinoma'/exp OR 'non clear cell renal cell carcinoma'/exp OR ((('kidney cell*' OR 'renal cell*' OR nephroid OR hypernephroid OR 'collecting duct') NEAR/3 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR mass*)):ti,ab,kw) OR ((grawitz* NEAR/3 (tumor* OR tumour*)):ti,ab,kw) OR hypernephroma*:ti,ab,kw OR 'hyper nephroma*':ti,ab,kw OR rcc:ti,kw OR mrcc:ti,kw OR nccrcc:ti,ab,kw OR ncrcc:ti,ab,kw	82999
	#2	'metastasis'/exp OR 'advanced cancer'/exp OR advanced:ti,ab,kw OR metastat*:ti,ab,kw OR mrcc:ti,ab,kw	1521720
	#3	'cytoreductive nephrectomy'/exp OR ((cytoreductive NEAR/3 nephrectom*):ti,ab,kw) OR 'artificial embolization'/exp OR embolization*:ti,ab,kw OR embolisation*:ti,ab,kw	126318
	#4	#1 AND #2 AND #3 AND ([english]/lim OR [dutch]/lim) AND [2017-2022]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference	407

		abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	
	#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	786647
	#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	3511032
	#7	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw)	13012374

	OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab))) #8 #4 AND #5 **– SR's** 36 #9 #4 AND #6 NOT #8 **– RCT's** 55 #10 #4 AND #7 NOT (#8 OR #9) **– observationele studies** 158 #11 #8 OR #9 OR #10 249
Medline (OVID)	1 exp Carcinoma, Renal Cell/ or exp Kidney Neoplasms/ or (('kidney' or 'renal' or nephroid or hypernephroid or 'collecting duct') adj3 (cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or mass*)).ti,ab,kf. or (grawitz* adj3 (tumor* or tumour*)).ti,ab,kf. or hypernephroma*.ti,ab,kf. or (RCC or MRCC or nccrcc or ncrcc).ti,ab,kf. (113490) 2 (exp Neoplasm Metastasis/ or (advanced or metastat* or mrcc).ti,ab,kf. (855414) 3 exp Cytoreduction Surgical Procedures/ or ((cytoreductive adj3 nephrectom*) or (embolization* or embolisation*)).ti,ab,kf. (58300) 4 1 and 2 and 3 (924) 5 limit 4 to ((english or dutch) and yr="2017 -Current") (340) 6 5 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (317) 7 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*))

	and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) (582771) 8 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (1363378) 9 Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) (5119665) 10 6 and 7 (21) **– SRs** 11 (6 and 8) not 10 (37) **- RCTs** 12 (6 and 9) not (10 or 11) (125) **– observationele studies** 13 10 or 11 or 12 (183)

Bijlagen bij module 6

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Overweeg en bespreek de voor- en nadelen van adjuvante therapie met pembrolizumab bij patiënten met heldercellig niercelcarcinoom en een TNM stadium die voldoen aan de inclusiecriteria van de Keynote 564 studie. • gemiddeld tot hoog (tumorstadium T2 met nucleaire graad 4 of sarcomatoïde kenmerken, of tumorstadium T3; geen regionale lymfeklieren of	1-3 jaar	Niet bekend, maar naar inschatting neutraal	bekendmaking richtlijn	Gebrek aan kennis over module	bekendmaken richtlijn	NVU, NIV NVRO	

metastasen op afstand aanwezig), • hoog (tumorstadium T4 zonder regionale lymfeklieren of metastasen op afstand, of elk tumorstadium met aanwezigheid van betrokkenheid van regionale lymfeklieren), of • stadium M1 NED (geen bewijs van ziekte).							
Gebruik gevalideerde risico scores (bijvoorbeeld Leibowich) bij patiënten met een heldercellig niercelcarcinoom pT3a ISUP/WHO graad 1 N0 M0 om hen bij laag of intermediair risico te wijzen op de gevaren van overbehandeling.	1-3 jaar	Niet bekend maar naar inschatting neutraal	bekendmaking richtlijn	-	bekendmaken richtlijn	NVU, NIV, NVRO	
Overweeg bij patiënten met een heldercellig	1-3 jaar	Niet bekend maar naar	bekendmaking richtlijn	-	bekendmaken richtlijn	NVU, NIV, NVRO	

niercelcarcinoom met een solitaire metachrone metastasering binnen 1 jaar na de nefrectomie beeldvorming na een interval van 3 maanden te herhalen alvorens tot metastasectomie over te gaan.		inschatting neutraal					

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, etc.

[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang.

Risk of Bias tables

Risk of bias table for intervention studies

Study reference (first author, year)	Was the allocation sequence adequately generated?	Was the allocation adequately concealed?	Blinding:	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?	Overall risk of bias

Motzer, 2013	**Definitely yes** **Reason: Authors used a computer-generated randomization schedule.**	**Definitely yes** **Reason: Authors used an interactive response technology system. Permuted blocks within each stratum.**	**Definitely yes** **Reason: Blinding of patients, physicians, physicians' staff (except pharmacist who prepared study drugs), and the study sponsor.**	**Definitely yes** **Reason: Most incomplete outcome data due to other reasons.**	**Definitely yes** **Reason: All outcomes reported in the trial registration are reported.**	**Probably yes** **Reason: Registered trial, industry sponsored trial (sponsor had a role in study design, data, analysis, interpretation and manuscript preparation, not in data collection).**	**Low risk of bias** **Reason: Correct randomization and blinding, registered RCT, but involvement of sponsoring industry.**
Choueiri, 2021; Choueiri, 2024 and Powles, 2022	**Definitely yes** **Reason: Authors used central permuted block randomization with an interactive voice-response system and interactive web-response system.**	**Definitely yes** **Reason: Authors used an interactive response technology system.**	**Definitely yes** **Reason: Blinding of patients and investigators (except pharmacist who prepared study drugs).**	**Definitely yes** **Reason: Most incomplete outcome data due to other reasons.**	**Definitely yes** **Reason: All outcomes reported in the trial registration are reported.**	**Probably yes** **Reason: Registered trial, industry sponsored trial (sponsor had a role in study design, data collection, analysis, interpretation and manuscript preparation).**	**Low risk of bias** **Reason: Correct randomization and blinding, registered RCT, but involvement of sponsoring industry.**
Pal, 2022	**Definitely yes** **Reason: Authors used an interactive voice-web response system.**	**Definitely yes** **Reason: Statistician created a predetermined randomization schedule.**	**Definitely yes** **Reason: Blinding of patients, study site personnel (except pharmacist and injecting physician), and the study sponsor.**	**Definitely yes** **Reason: Most incomplete outcome data due to other reasons.**	**Definitely yes** **Reason: All outcomes reported in the trial registration are reported.**	**Probably yes** **Reason: Registered trial, industry sponsored trial (sponsor had a role in study design, data collection, analysis, interpretation and manuscript preparation).**	**Low risk of bias** **Reason: Correct randomization and blinding, registered RCT, but involvement of sponsoring industry.**

Table of quality assessment for systematic reviews of RCTs and observational studies
Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Evidence tables

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Study	Appropriate and clearly focused question?[1]	Comprehensive and systematic literature search?[2]	Description of included and excluded studies?[3]	Description of relevant characteristics of included studies?[4]	Appropriate adjustment for potential confounders in observational studies?[5]	Assessment of scientific quality of included studies?[6]	Enough similarities between studies to make combining them reasonable?[7]	Potential risk of publication bias taken into account?[8]	Potential conflicts of interest reported?[9]
Riaz, 2021	Yes. Research question is described.	Yes. PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials were searched, and search period and strategy were reported.	Yes the included studies are described.	Yes. Characteristics were presented.	Not applicable.	Yes using MAGIC app.	Yes, clinical and statistical heterogeneity were considered.	Unclear. Less than 10 studies (5 in total) are included in the review. Therefore risk of publication bias cannot be adequately assessed.	Yes of all the authors but not the included studies.

Research question: What are the (un)desirable effects of (neo)adjuvant therapy compared to no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma?
P: patients with non-metastatic renal cell carcinoma
I: (neo)adjuvant therapy (sunitinib, cabozantinib, pazopanib, pembrolizumab, avelumab, ipilimumab, nivolumab)
C: no (neo)adjuvant therapy (placebo or observation)
O: disease-free survival, overall survival, quality of life, adverse events (toxicity)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Riaz, 2021 **[individual study characteristics deduced from [1st author, year of publication]]** **PS., study characteristics and results are extracted from the SR (unless stated otherwise)**	**SR and meta-analysis** ***Literature search up to February, 2021*** **6 23-25** **A: Eisen, 2020** **B: Motzer, 2018** **C: Staehler, 2018** **D: Motzer, 2021** **<u>Study design</u>:** **RCT** **<u>Setting and Country</u>:** **A: United Kingdom** **B: USA** **C: USA** **D: USA** **<u>Source of funding and conflicts of interest:</u>** **[non-commercial]** **Jeremy L. Warner** **Stock and Other Ownership Interests:** HemOnc.org **Consulting or Advisory Role:** Wolters, IBM **Travel, Accommodations, Expenses:** IBM **Manish Kohli** **Honoraria:** Advanced Accelerator Applications **Travel, Accommodations, Expenses:** Celgene No other potential conflicts of interest were reported.	**Inclusion criteria SR: Reports in peer-reviewed journals, abstracts, FDA documents, company summary information. Reports in any language. All RCTs comparing VEGF TKIs with placebo that reported DFS, OS, and safety data were included.** **Exclusion criteria SR:** ***4 studies included*** **<u>Important patient characteristics at baseline</u>:** ***Number of patients; characteristics important to the research***	**Describe intervention:** **S-TRAC: Sunitinib 50 mg once daily** **ASSURE: arm 1: Sunitinib 50 mg once daily, arm 2 Sorafenib 400 mg twice daily** **PROTECT: Pazopanib 800 mg (amended to 600 mg) once daily** **ATLAS: Axitinib 5 mg twice daily** **SORCE: arm 1: Sorafenib 400 mg twice daily for 1 year, followed by placebo for 2 years, arm 2: Sorafenib 400 mg twice daily for 3 years**	**Describe control:** **S-TRAC: placebo once daily** **ASSURE: arm 1: placebo once daily, arm 2: placebo twice daily** **PROTECT: placebo once daily** **ATLAS: placebo twice daily** **SCORCE: arm 1: placebo twice daily.**	**<u>End-point of follow-up</u>:** **S-TRAC: 12.4 months** **ASSURE: approximately 12 months** **PROTECT: 10.4 months** **ATLAS: NA** **SCORCE: arm 1: 11.7 months, arm 2: 10.6 months** **<u>For how many participants were no complete outcome data available?</u> (intervention/control)** **S-TRAC: control: 30, treatment: 44** **ASSURE: control: 29, arm 1: 52, arm 2: 50** **PROTECT: control: 27, treatment: 51** **ATLAS: control: 28, treatment: 31** **SCORCE: control: 26, arm 1: 49, arm 2: 50**	**<u>Outcome measure-1</u>** **Overall survival (OS)** **Random effects model: HR [95% CI]** **S-TRAC: 0.92 [0.66 to 1.28]** **ASSURE_Suni: 1.06 [0.84 to 1.34]** **ASSURE_Sora: 1.03 [0.88 to 1.22]** **PROTECT: 1.02 [0.90 to 1.17]** **ATLAS: 1.02 [0.90 to 1.16]** **SCORCE_1 y: 1.00 [0.89 to 1.12]** **SCORCE_3 y: 1.01 [0.91 to 1.12]** **<u>Outcome measure-2</u>** **Defined as disease-free survival (DFS)** **Random effects model: HR [95% CI]** **S-TRAC: 0.76 [0.59 to 0.98]** **ASSURE_Suni: 0.89 [0.67 to 1.19]** **ASSURE_Sora: 0.93 [0.79 to 1.09]**	**<u>Risk of bias (high, some concerns or low):</u>** **<u>See figure below.</u>**  **<u>Facultative</u>:** **Brief description of author's conclusion** **There is no guidance on when to stop maintaining a living review. In this example we used trial sequential analysis and high certainty of evidence (future clinical trials unlikely to change current conclusions) as a benchmark to conclude a living review in view of convincing evidence. Overall these results are consistent with previous analyses.** **Personal remarks on study quality, conclusions, and other issues (potentially)**

		question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ... **<u>N, mean age</u>** **S-TRAC: n=615, median age= 58** **ASSURE: n=1943, median age= 56** **PROTECT: n=1538, median age= 59** **ATLAS: n=724, median age = 58** **SORCE: n=1711, median age = 58** ***<u>Sex</u>:*** **S-TRAC= 74% male** **ASSURE= 67% male** **PROTECT= 72% male** **ATLAS= 73% male** **SORCE= 71% male** **Groups comparable at baseline? Yes**				**PROTECT: 0.90 [0.80 to 1.02]** **ATLAS: 0.90 [0.81 to 0.99]** **SCORCE_1 y: 0.91 [0.84 to 0.99]** **SCORCE_3 y: 0.92 [0.86 to 1.00]** **<u>Outcome measure-3</u>** **all-cause adverse event (AE) of any grade** **Random effects model: RR [95% CI]** **S-TRAC: 1.13 [1.08 to 1.17]** **ASSURE_Suni: -** **ASSURE_Sora: -** **PROTECT: 1.12 [1.09 to 1.14]** **ATLAS: 1.10 [1.08 to 1.13]** **SCORCE_1 y: 1.08 [1.02 to 1.15]** **SCORCE_3 y: 1.07 [1.02 to 1.12]** **<u>Outcome measure-4</u>** **all-cause adverse event (AE) of grade ≥3** **Random effects model: RR [95% CI]**	**relevant to the research question** **Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading** **Sensitivity analyses (excluding small studies; excluding studies with short follow-up; excluding low quality studies; relevant subgroup-analyses); mention only analyses which are of potential importance to the research question** **Heterogeneity: clinical and statistical heterogeneity; explained versus unexplained (subgroupanalysis)**

						S-TRAC: 2.92 [2.32 to 3.67] **ASSURE_Suni: 2.63 [2.26 to 3.06]** **ASSURE_Sora: 2.69 [2.45 to 2.96]** **PROTECT: 2.75 [2.54 to 2.98]** **ATLAS: 2.60 [2.29 to 2.96]** **SCORCE_1 y: 2.49 [2.17 to 2.86]** **SCORCE_3 y: 2.44 [2.17 to 2.76]** **<u>Outcome measure-5</u>** **treatment-related adverse events (trAEs) of any grade** **Random effects model: RR [95% CI]** **S-TRAC: 1.30 [1.22 to 1.39]** **ASSURE_Suni: -** **ASSURE_Sora: -** **PROTECT: -** **ATLAS: 1.45 [1.15 to 1.83]** **SCORCE_1 y: -** **SCORCE_3 y: -** **<u>Outcome measure-5</u>** **treatment-related adverse events (trAEs) of grade ≥3**	

						Random effects model: RR [95% CI] **S-TRAC: 6.95 [4.72 to 10.25]** **ASSURE_Suni: -** **ASSURE_Sora: -** **PROTECT: -** **ATLAS: 5.25 [3.10 to 8.88]** **SCORCE_1 y: -** **SCORCE_3 y: -**	

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies [cohort studies, case-control studies, case series])[1]
This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question:

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Motzer, 2013	Type of study: Multicentre, randomised, double-blind, phase 3 trial. Setting and country: Funding: Bristol Myers Squibb and Ono Pharmaceutical. Conflicts of interest: Many	In-/ exclusion criteria - age ≥ 18 years - localized renal cell carcinoma with a predominantly clear cell histology - high risk of relapse - partial or radical nephrectomy - negative surgical margins with no clinical or radiological evidence of macroscopic residual disease or distant metastases after nephrectomy - ECOG performance status of 0 or 1 - TNM stage pT2aN0M0, pT2b,N0M0, pT3N0M0, pT4N0M0, or pT4N1M0 - no previous systemic therapy for renal cell carcinoma - no malignancy ≤3 years ago (except locally cured cancer) - other exclusion criteria related to a suppressed immune status N total at baseline: 816 Intervention: 405	Nivolumab (240 mg) intravenously every 2 weeks for 12 doses plus ipilimumab (1 mg/kg) intravenously every 6 weeks for four doses.	Placebo intravenously every 2 weeks for 12 doses plus placebo intravenously every 6 weeks for four doses.	Length of follow-up: Median 37.0 months (IQR 31.3 – 43.7) Incomplete outcome data: Intervention: 173 (42.7%) - 132 study drug toxicity - 11 disease recurrence - 8 adverse event - 8 patients' decision - 3 consent withdrawal - 1 death - 1 poor / no compliance - 9 COVID Control: 46 (11.2%) - 5 study drug toxicity - 20 disease recurrence	Median time of disease-free survival: I: not reached C: 50.7 months (48.1 to not estimable) HR 0.92 (95% CI 0.71 - 1.19, p=0.53) Overall survival: Not reached. I: 33 events C: 28 events	Name of study: CheckMate 914

		Control:411 Important prognostic factors[2]: Age, median (IQR): I: 58 (51 – 65) C: 57 (50 – 65) Sex: I: 71% male C: 72% male Disease risk category: I: 56% high risk, 43% moderate risk, <1% other C: 57% high risk, 43% moderate risk, <1% other			- 4 adverse event - 4 patients' decision - 4 consent withdrawal - 1 lost to follow-up - 1 pregnancy - 7 other		
Choueiri, 2021; Choueiri, 2024 and Powles, 2022	Type of study: Multicentre, randomised, double-blind, phase 3 trial. Setting and country: 213 sites in 21 countries. Funding: Merck Sharp and Dohme, a subsidiary of Merck. Conflicts of interest: Many	In-/ exclusion criteria - age ≥ 18 years - renal cell carcinoma with a clear cell component - intermediate or high risk of recurrence - partial or radical nephrectomy or metastectomy with negative surgical margins ≤12 weeks of randomization - ECOG performance status of 0 or 1 - no evidence of disease at screening - no previous systemic therapy for renal cell carcinoma N total at baseline: 994 Intervention: 496 Control:498 Important prognostic factors[2]: Age, median (range): I: 60.0 (27 – 81) C: 60.0 (25 – 84) Sex: I: 70% male C: 72.1% male Disease risk category: I: 86.1% M0 intermediate-to-high risk, 8.1% M0 high risk, 5.8% M1. C: 86.9% M0 intermediate-to-high risk, 7.2% M0 high risk, 5.8% M1. PD-L1 immune cell expression: I: 25% <1%, 73.6% ≥1% C: 22.7% <1%, 76.9% ≥1%	Pembrolizumab 200 mg intravenously every 3 weeks for up to 17 cycles or until a new malignancy or any progression or recurrence of the malignancy under study occurred, the participant or physician decided to discontinue treatment, or any occurrence of pregnancy, intercurrent illness, or recurrent grade 2 or worse pneumonitis.	Placebo intravenously every 3 weeks for up to 17 cycles or until a new malignancy or any progression or recurrence of the malignancy under study occurred, the participant or physician decided to discontinue treatment, or any occurrence of pregnancy, intercurrent illness, or recurrent grade 2 or worse pneumonitis.	Length of follow-up: Choueiri 2021: 24.1 months Powles 2022: 30.1 months (IQR 25.7 - 36.7). Incomplete outcome data: Intervention: 38.9% - 21.3% adverse event - 10.5% disease recurrence - other not reported Control: 26.2% - 20.4% disease recurrence - other not reported	Disease-free survival at data-cutoff: I: 109 events C: 151 events Risk of disease recurrence or death: Choueiri 2021: HR 0.68 (95% CI 0.53 – 0.87, p=0.002) Powles 2022: HR 0.63 (95% CI 0.50 – 0.80) Overall survival: Choueiri 2021: I: 18 events C: 33 events HR 0.54 (95% CI 0.30 – 0.96) Powles 2022: HR 0.52 (95% CI 0.31 – 0.86) 30-month survival rate: I: 95.7% (95% CI 93.3 - 97.2)	Name of study: KEYNOTE-564 Median disease-free survival and overall survival were not reached. Data update of 2024 is presented in 'Overweginge n'

						C: 91.4% (95% CI 88.3 - 93.7)	
Pal, 2022	Type of study: Multicentre, randomised, double-blind, phase 3 trial. Setting and country: 215 centres in 28 countries or regions. Funding: F Hoffmann-La Roche and Genentech, a member of the Roche group. Conflicts of interest: Many	In-/ exclusion criteria: - age ≥ 18 years - renal cell carcinoma with a clear cell or sarcomatoid component - increased risk of recurrence - nephrectomy with or without metastectomy ≤12 weeks of randomization - ECOG performance status of 0 or 1 - no evidence of disease at screening - no previous anticancer therapy for renal cell carcinoma N total at baseline: 778 Intervention: 390 Control:388 Important prognostic factors[2]: Age, median (IQR): I: 60.5 (52.0 – 69.0) C: 60.0 (52.8 – 68.0) Sex: I: 74% male C: 72% male Disease stage: I: 65% T2 or T3a, 21% T3-c or T4 or N+, 14% no evidence of disease, 15% metastasis. C: 64% T2 or T3a, 23% T3-c or T4 or N+, 13% no evidence of disease, 13% metastasis. PD-L1 immune cell expression: I: 41% <1%, 59% ≥1% C: 39% <1%, 61% ≥1%	Atezolizumab 1200 mg intravenously once every 3 weeks for 16 cycles or 1 year (whichever occurred first), or until disease recurrence, unacceptable toxicity, intercurrent illness that might affect patient safety with continued treatment, pregnancy, withdrawal of consent, or study termination by the sponsor.	Placebo intravenously every 3 weeks for 16 cycles or 1 year (whichever occurred first), or until disease recurrence, unacceptable toxicity, intercurrent illness that might affect patient safety with continued treatment, pregnancy, withdrawal of consent, or study termination by the sponsor.	Length of follow-up: Median: 44.7 months (IQR 39.1 – 51.0) Incomplete outcome data: Intervention: 135 (34.6%) - 51 disease relapse - 45 adverse events - 20 consent withdrawal - 16 other reasons - 2 physician decision - 1 death Control: 109 (28.1%) - 60 disease relapse - 10 adverse events - 12 consent withdrawal - 25 other reasons - 1 physician decision - 1 death	Disease-free survival assessed by investigators: I: 42%, 164 events C: 43%, 168 events Median time of disease-free survival: I: 57.2 months (44.6 to not estimable) C: 49.5 months (47.4 to not estimable) HR 0.93 (95% CI 0.75 - 1.15, p=0.50) Overall survival: I: 14%, 54 events C: 14%, 53 events 3-year survival: I: 90.3% (95% CI 87.3 - 93.3) C: 89.8% (95% CI 86.6 - 92.9)	Name of study: Mmotion010 The primary endpoint of the study was not met.

Notes:

1. Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures
2. Provide data per treatment group on the most important prognostic factors [(potential) confounders]
3. For case-control studies, provide sufficient detail on the procedure used to match cases and controls
4. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

Literature search strategy

Embase

Zoektermen		
No.	*Query*	*Results*
#1	('renal cell carcinoma'/exp/mj OR 'non clear cell renal cell carcinoma'/exp/mj OR ((('kidney cell*' OR 'renal cell*' OR nephroid OR hypernephroid OR 'collecting duct') NEAR/3 (cancer* OR carcinoma* OR adenocarcinoma* OR neoplasm* OR tumor* OR tumour* OR mass*)):ti,ab,kw) OR ((grawitz* NEAR/3 (tumor* OR tumour*)):ti,ab,kw) OR hypernephroma*:ti,ab,kw OR 'hyper nephroma*':ti,ab,kw OR rcc:ti,kw OR nccrcc:ti,kw OR ncrcc:ti,kw) NOT ((metastatic:ti OR advanced:ti) NOT ('non metastatic':ti OR nonmetastatic:ti))	63472
#2	'sunitinib'/exp/mj OR 'cabozantinib'/exp OR 'pazopanib'/exp OR 'nivolumab'/exp OR 'pembrolizumab'/exp OR 'ipilimumab'/exp OR 'avelumab'/exp OR sunitinib:ti,ab,kw OR cabozantinib:ti,ab,kw OR pazopanib:ti,ab,kw OR nivolumab:ti,ab,kw OR pembrolizumab:ti,ab,kw OR ipilimumab:ti,ab,kw OR avelumab:ti,ab,kw OR adjuvant:ti,kw	134562
#3	#1 AND #2 AND ([english]/lim OR [dutch]/lim) AND [2019-2022]/py NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('conference abstract'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	1053
#5	'meta analysis'/de OR 'meta analysis (topic)'/exp OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de	606845
#6	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1902965
#7	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR	12774067

	crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#8	#3 AND #5 **– SR's**	67
#9	#3 AND #6 NOT #8 **– RCT's**	71
#10	#3 AND #7 NOT (#8 OR #9) **– observationele studies**	379
#11	#8 OR #9 OR #10	517

Medline (OVID)

Zoektermen
1 (exp Carcinoma, Renal Cell/ or exp Kidney Neoplasms/ or (('kidney' or 'renal' or nephroid or hypernephroid or 'collecting duct') adj3 (cancer* or carcinoma* or adenocarcinoma* or neoplasm* or tumor* or tumour* or mass*)).ti,ab,kf. or (grawitz* adj3 (tumor* or tumour*)).ti,ab,kf. or hypernephroma*.ti,ab,kf. or (RCC or MRCC or nccrcc or ncrcc).ti,ab,kf.) not ((metastatic.ti. or advanced.ti.) not (non-metastatic or nonmetastatic).ti.) (104585)
2 exp *Chemotherapy, Adjuvant/ or exp *Neoadjuvant Therapy/ or exp *Sunitinib/ or exp *Nivolumab/ or exp *Ipilimumab/ or adjuvant.ti,kf. or neoadjuvant.ti,kf. or sunitinib.ti,ab,kf. or pazopanib.ti,ab,kf. or nivolumab.ti,ab,kf. or (ipilimumab or pembrolizumab or avelumab or cabozantinib).ti,ab,kf. (85291)
3 1 and 2 (2834)
5 limit 3 to ((english or dutch) and yr="2019 -Current") (901)
6 5 not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/)) (845)
7 (meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or

cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) (588379)

8 (exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/) (1370304)

9 Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) (5140446)

10 6 and 7 (48) **– SRs**

11 (6 and 8) not 10 (60) **- RCTs**

12 (6 and 9) not (10 or 11) (157) **– observationele studies**

13 10 or 11 or 12 (265)