Herziening Richtlijn Niercelcarcinoom

INITIATIEF
Nederlandse Vereniging voor Urologie

IN SAMENWERKING MET
Nederlandse Internisten Vereniging
Nederlandse Vereniging voor Medische Oncologie
Nederlandse Vereniging voor Interventieradiologie
Nederlandse Vereniging voor Radiologie
Nederlandse Vereniging voor Radiotherapie en Oncologie
Verpleegkundigen & Verzorgenden Nederland
Nederlandse Federatie van Kankerpatiëntenorganisaties
Patiëntenvereniging Blaas- of Nierkanker

MET ONDERSTEUNING VAN
Het Kennisinstituut van de Federatie Medisch Specialisten

FINANCIERING
De richtlijnontwikkeling werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS).

Colofon
RICHTLIJN NIERCELCARCINOOM
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Startpagina – Niercelcarcinoom

Waar gaat deze richtlijn over?
Deze richtlijn richt zich op wat volgens de huidige maatstaven de beste zorg is voor patiënten met nierkanker. In de herziene richtlijn komen de volgende onderwerpen aan de orde:

- Behandeling van T1b niertumoren
- Keuze eerstelijns systemische therapie heldercellig niercelcarcinoom Optimale eerstelijns systeemtherapie niet-heldercellig niercelcarcinoom
- Oligometastasering
- Cytoreductieve therapie gecombineerd met systemische therapie
- Adjuvante behandeling

Voor wie is deze richtlijn bedoeld?
Deze richtlijn is bestemd voor alle zorgverleners die betrokken zijn bij de zorg voor patiënten met nierkanker. De richtlijn geldt dus met name voor urologen en internist oncologen, maar ook voor andere medisch specialisten zoals pathologen, (interventie-)radiologen, radiotherapeuten, neurologen, neurochirurgen, orthopeden, thoraxchirurgen en verpleegkundig specialisten in de tweede- en derdelijnszorg die betrokken zijn bij de behandeling van patiënten met niertumoren in Nederland. Daarnaast moeten ook verpleegkundigen en patiënten aanknopingspunten kunnen vinden in de richtlijn.

Voor patiënten
Niercelcarcinoom is de medische term voor nierkanker. In Nederland krijgen jaarlijks ongeveer 2800 mensen nierkanker. Klachten die kunnen ontstaan zijn: bloed in de urine, pijn in de zij en een voelbare massa in de buik. De enig genezende behandeling is een operatie. Genezing is echter niet altijd haalbaar. Er zijn verschillende operaties mogelijk, welke de voorkeur heeft, hangt af van de grootte en uitgebreidheid van de tumor. Het is belangrijk dat alle mogelijke behandelopties (ook niet behandelen en eventueel afwachten) met patiënten en naasten worden besproken. De voor- en nadelen, ook de gevolgen op de lange termijn en wat voor de patiënt belangrijk is in het leven. Om zo in een proces van samen beslissen tot een weloverwogen keuze te komen.

Hoe is de richtlijn tot stand gekomen?
Het initiatief voor deze richtlijn is afkomstig van Nederlandse Vereniging voor Urologie (NVU). De richtlijn is opgesteld door een multidisciplinaire commissie met vertegenwoordigers vanuit de oncologen, urologen, pathologen, radiologen, radiotherapeuten verpleegkundig specialisten en epidemiologen. Voor het opstellen van de richtlijn is een knelpunteninventarisatie gehouden bij professionals en patiënten(vertegenwoordigers).

Status van de richtlijn
Deze richtlijn wordt modulair herzien. In de laatste herziening (2024) zijn de volgende modules herzien/ontwikkeld:

- Behandeling van T1b niertumoren
- Keuze eerstelijns systemische therapie heldercellig niercelcarcinoom Optimale eerstelijns systeemtherapie niet-heldercellig niercelcarcinoom
- Oligometastasering
- Cytoreductieve therapie gecombineerd met systemische therapie
- Adjuvante behandeling

Verantwoording

Leeswijzer
[Deze verantwoording zal op de Richtlijnendatabase (Richtlijnendatabase.nl) bij elk van de in deze richtlijn opgenomen modules worden geplaatst.]

Autorisatie en geldigheid

Autorisatiedatum:	*Volgt nog*
Eerstvolgende beoordeling actualiteit	2025 (binnen cluster Uro-oncologie)
Geautoriseerd door:	*Volgt nog*
Belangrijkste wijzigingen t.o.v. vorige versie:	Uit de NVU richtlijn Niercelcarcinoom (2010), welke al in 2021 geupdate is met 8 modules,zijn de volgende modules modulair gemaakt: 1. Behandeling van T1b niertumoren 2. 2. Keuze eerstelijns systemische therapie heldercellig niercelcarcinoom Optimale eerstelijns systeemtherapie niet-heldercellig niercelcarcinoom 3. Oligometastasering 4. Cytoreductieve therapie gecombineerd met systemische therapie 5. Adjuvante behandeling
Regiehouder(s):	NVU

Algemene gegevens
De ontwikkeling/herziening van deze richtlijnmodule werd ondersteund door het Kennisinstituut van de Federatie Medisch Specialisten (www.demedischspecialist.nl/kennisinstituut) en werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS).
De financier heeft geen enkele invloed gehad op de inhoud van de richtlijnmodule.

Samenstelling werkgroep
Voor het ontwikkelen van de richtlijnmodule is in 2021 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen (zie hiervoor de Samenstelling van de werkgroep) die betrokken zijn bij de zorg voor patiënten met nierkanker en een vertegenwoordiger namens de patiëntenvereniging.

Belangenverklaringen
De Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden hebben schriftelijk verklaard of zij in de laatste drie jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatiemanagement) hebben gehad. Gedurende de ontwikkeling of herziening van een module worden wijzigingen in belangen aan de voorzitter doorgegeven. De belangenverklaring wordt opnieuw bevestigd tijdens de commentaarfase.
Een overzicht van de belangen van werkgroepleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten.

Werkgroeplid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Bex (voorzitter)	Uroloog AVL Amsterdam. Afdelingshoofd in het Specialist Centre of Kidney Cancer, Royal Free London NHS Foundation Trust, Professor of Urology, UCL Division of Surgery and Investigational Science.	Alle nevenfuncties zijn onbetaald: Vice Chair EAU renal cancer guideline.	- Restricted educational grant van Pfizer tbv een neoadjuvante studie (sponsor is het NKI-AvL). - Steering committee op twee internationale adjuvante fase 3 studies van BMS en Roche. - Lid van medical steering committee van twee patientenorganisaties (Kidney Cancer Association en IKCC). - Financier BMS: randomised phase 3 trial of adjuvant nivolumab plus ipilimumab versus placebo in high risk RCC. - Financier Roche: randomised phase 3 trial of adjuvant atezolizumab versus placebo in high risk RCC. - Financier Pfizer: single-arm phase 2 trial of neoadjuvant avelumab plus axitinib in high risk RCC (funded by restricted educational grant)	Geen restricties
Bevers	Uroloog LUMC Leiden	Geen	Geen	Geen restricties
Langenhuijsen	Uroloog Radboudumc Nijmegen	Invited speaker Update Urology (Astra Zeneca), vergoeding+reiskosten	Financier: ZonMW Voorbereidende studie Doelmatigheidsonderzoek, Pentixafor PET vs veneuze sampling bij primair hyperaldosteronisme - Financier: PentixaPharm GmbH, CASTUS trial.	Geen restricties
Hamberg	Oncoloog Franciscus Gasthuis en Vlietland Rotterdam	voorzitter WIN-O nier (onbetaald) bestuurslid Pro RCC (onbetaald)	- Adviesraden meerdere farmaceutische bedrijven actief binnen RCC zorg - lokale hoofonderzoeker van aantal adjuvante nierkanker studies (Farma sponsored). Tevens ook van studies (farma sponsored) naar medicamenteuze interventies bij gemetastaseerde ziekte (oa RCC)	Geen restricties
Van Thienen	Internist-oncoloog NKI-AvL Amsterdam	Alle nevenfuncties zjn onbetaald: - Inhoudelijk/vice voorzitter Medisch Inhoudelijke Standpunten (MIS) groep van DRCG	Pfizer Neoadjuvant axitinib en avelumab bij niercelcarcinoom (projectleider); BMS Checkmate 914 Adjuvant immunotherapy in high-risk renal cancer	Geen restricties

		- Lid wetenschappelijke adviesraad Stichting PRO-RCC	(onderzoeker); Eisai CLEAR study: levantinib and everolimus or pembrolizumab vs sunitinib in mRCC (onderzoeker); Goethe University Frankfurt am Main Sunniforecast (nivolumab+ipilimumab vs sunitinib in non-clear cell mRCC)(onderzoeker); Roche Adjuvant atezolizumab in high risk renal cancer (onderzoeker)	
Bloos-van der Hulst	Verpleegkundig specialist uro-oncologie AVL Amsterdam	Geen	Geen	Geen restricties
Kerkmeijer	Radiotherapeut-oncoloog, Radboudumc Nijmegen. Plaatsvervangend keteneigenaar Urologische Oncologie Radboudumc Nijmegen	Alle nevenfuncties zjn onbetaald: - DUOS bestuurslid - Raad van Advies Tie Ribbon - Associate Editor Frontiers in oncology - Radiotherapeut-oncoloog UMC Utrecht (gastaanstelling)	KWF subsidie FLAME studie prostaatcarcinoom	Geen restricties
Wolak	Belangenbehartiger kwaliteit van zorg Patiëntenvereniging blaas- of nierkanker (PBNK)	Patiëntenvereniging blaas- of nierkanker	Werkzaam bij patiëntenorganisatie Leven met blaas- of nierkanker, geen boegbeeldfunctie	Geen restricties
Meier	Interventieradioloog Isala Zwolle Voorzitter RVE Medische Beeldvorming, Isala Zwolle		Geen	Geen restricties
Bruynzeel	Radiotherapeut-oncoloog, Amsterdam UMC	Geen	ViewRay Inc: Een onderzoek naar hoge en precieze bestraling (stereotactische ablatieve radiotherapie) bij patiënt	Geen restricties

Inbreng patiëntenperspectief

Er werd aandacht besteed aan het patiëntenperspectief door uitnodigen van de Patiëntenvereniging blaas- of nierkanker (PBNK) voor de schriftelijke knelpunteninventarisatie en afvaardiging namens PBNK in de werkgroep. De verkregen input is meegenomen bij het opstellen van de uitgangsvragen, de keuze voor de uitkomstmaten en bij het opstellen van de overwegingen (zie per module ook “Waarden en voorkeuren van patiënten”). De conceptrichtlijn is tevens voor commentaar voorgelegd aan Patiëntenvereniging blaas- of nierkanker (PBNK) en de eventueel aangeleverde commentaren zijn bekeken en verwerkt.

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule is conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uitgevoerd om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema op de Richtlijnendatabase).

Module	**Uitkomst raming**	**Toelichting**
Module Behandeling van T1b niertumoren	geen financiële gevolgen	Uitkomst 1

Module	**Uitkomst raming**	**Toelichting**
Module Systemische therapie	geen financiële gevolgen	Uitkomst 1

Module	**Uitkomst raming**	**Toelichting**
Module Optimale eerstelijns systeemtherapie niet-heldercellig niercelcarcinoom	geen financiële gevolgen	Uitkomst 1

Module	**Uitkomst raming**	**Toelichting**
Module Oligometastasering	geen financiële gevolgen	Uitkomst 1

Module	**Uitkomst raming**	**Toelichting**
Module Cytoreductieve therapie gecombineerd met systemische therapie	geen financiële gevolgen	Uitkomst 1

Module	**Uitkomst raming**	**Toelichting**
Module Adjuvante behandeling	geen financiële gevolgen	Uitkomst 1

De kwalitatieve raming volgt na de commentaarfase.

Werkwijze

AGREE

Deze richtlijnmodule is opgesteld conform de eisen vermeld in het rapport Medisch Specialistische Richtlijnen 3.0 van de adviescommissie Richtlijnen van de Raad Kwaliteit. Dit rapport is gebaseerd op het AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers, 2010).

Knelpuntenanalyse en uitgangsvragen

Tijdens de voorbereidende fase inventariseerde de werkgroep de knelpunten in de zorg voor patiënten met nierkanker. Tevens zijn er knelpunten aangedragen door de NVU (Nederlandse Vereniging voor Urologie) en NVRO, NVVR en Patiëntenvereniging blaas- of nierkanker (PBNK) via een schriftelijke knelpuntenanalyse.

Op basis van de uitkomsten van de knelpuntenanalyse zijn door de werkgroep concept-uitgangsvragen opgesteld en definitief vastgesteld.

Uitkomstmaten

Na het opstellen van de zoekvraag behorende bij de uitgangsvraag inventariseerde de werkgroep welke uitkomstmaten voor de patiënt relevant zijn, waarbij zowel naar gewenste als ongewenste effecten werd gekeken. Hierbij werd een maximum van acht uitkomstmaten gehanteerd. De werkgroep waardeerde deze uitkomstmaten volgens hun relatieve belang bij de besluitvorming rondom aanbevelingen, als cruciaal (kritiek voor de besluitvorming), belangrijk (maar niet cruciaal) en onbelangrijk. Tevens definieerde de werkgroep tenminste voor de cruciale uitkomstmaten welke verschillen zij klinisch (patiënt) relevant vonden.

Methode literatuursamenvatting

Een uitgebreide beschrijving van de strategie voor zoeken en selecteren van literatuur is te vinden onder 'Zoeken en selecteren' onder Onderbouwing. Indien mogelijk werd de data uit verschillende studies gepoold in een random-effects model. Review Manager 5.4 werd gebruikt voor de statistische analyses. De beoordeling van de kracht van het wetenschappelijke bewijs wordt hieronder toegelicht.

Beoordelen van de kracht van het wetenschappelijke bewijs

De kracht van het wetenschappelijke bewijs werd bepaald volgens de GRADE-methode. GRADE staat voor 'Grading Recommendations Assessment, Development and Evaluation' (zie http://www.gradeworkinggroup.org/). De basisprincipes van de GRADE-methodiek zijn: het benoemen en prioriteren van de klinisch (patiënt) relevante uitkomstmaten, een systematische review per uitkomstmaat, en een beoordeling van de bewijskracht per uitkomstmaat op basis van de acht GRADE-domeinen (domeinen voor downgraden: risk of bias, inconsistentie, indirectheid, imprecisie, en publicatiebias; domeinen voor upgraden: dosis-effect relatie, groot effect, en residuele plausibele confounding).
GRADE onderscheidt vier gradaties voor de kwaliteit van het wetenschappelijk bewijs: hoog, redelijk, laag en zeer laag. Deze gradaties verwijzen naar de mate van zekerheid die er bestaat over de literatuurconclusie, in het bijzonder de mate van zekerheid dat de literatuurconclusie de aanbeveling adequaat ondersteunt (Schünemann, 2013; Hultcrantz, 2017).

GRADE	Definitie
Hoog	• er is hoge zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • het is zeer onwaarschijnlijk dat de literatuurconclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Redelijk	• er is redelijke zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • het is mogelijk dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.

Laag	• er is lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • er is een reële kans dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Zeer laag	• er is zeer lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; • de literatuurconclusie is zeer onzeker.

Bij het beoordelen (graderen) van de kracht van het wetenschappelijk bewijs in richtlijnen volgens de GRADE-methodiek spelen grenzen voor klinische besluitvorming een belangrijke rol (Hultcrantz, 2017). Dit zijn de grenzen die bij overschrijding aanleiding zouden geven tot een aanpassing van de aanbeveling. Om de grenzen voor klinische besluitvorming te bepalen moeten alle relevante uitkomstmaten en overwegingen worden meegewogen. De grenzen voor klinische besluitvorming zijn daarmee niet één op één vergelijkbaar met het minimaal klinisch relevant verschil (Minimal Clinically Important Difference, MCID). Met name in situaties waarin een interventie geen belangrijke nadelen heeft en de kosten relatief laag zijn, kan de grens voor klinische besluitvorming met betrekking tot de effectiviteit van de interventie bij een lagere waarde (dichter bij het nuleffect) liggen dan de MCID (Hultcrantz, 2017).

Overwegingen (van bewijs naar aanbeveling)

Om te komen tot een aanbeveling zijn naast (de kwaliteit van) het wetenschappelijke bewijs ook andere aspecten belangrijk en worden meegewogen, zoals aanvullende argumenten uit bijvoorbeeld de biomechanica of fysiologie, waarden en voorkeuren van patiënten, kosten (middelenbeslag), aanvaardbaarheid, haalbaarheid en implementatie. Deze aspecten zijn systematisch vermeld en beoordeeld (gewogen) onder het kopje 'Overwegingen' en kunnen (mede) gebaseerd zijn op expert opinion. Hierbij is gebruik gemaakt van een gestructureerd format gebaseerd op het evidence-to-decision framework van de internationale GRADE Working Group (Alonso-Coello, 2016a; Alonso-Coello 2016b). Dit evidence-to-decision framework is een integraal onderdeel van de GRADE methodiek.

Formuleren van aanbevelingen

De aanbevelingen geven antwoord op de uitgangsvraag en zijn gebaseerd op het beschikbare wetenschappelijke bewijs en de belangrijkste overwegingen, en een weging van de gunstige en ongunstige effecten van de relevante interventies. De kracht van het wetenschappelijk bewijs en het gewicht dat door de werkgroep wordt toegekend aan de overwegingen, bepalen samen de sterkte van de aanbeveling. Conform de GRADE-methodiek sluit een lage bewijskracht van conclusies in de systematische literatuuranalyse een sterke aanbeveling niet a priori uit, en zijn bij een hoge bewijskracht ook zwakke aanbevelingen mogelijk (Agoritsas, 2017; Neumann, 2016). De sterkte van de aanbeveling wordt altijd bepaald door weging van alle relevante argumenten tezamen. De werkgroep heeft bij elke aanbeveling opgenomen hoe zij tot de richting en sterkte van de aanbeveling zijn gekomen.

In de GRADE-methodiek wordt onderscheid gemaakt tussen sterke en zwakke (of conditionele) aanbevelingen. De sterkte van een aanbeveling verwijst naar de mate van zekerheid dat de voordelen van de interventie opwegen tegen de nadelen (of vice versa), gezien over het hele spectrum van patiënten waarvoor de aanbeveling is bedoeld. De sterkte van een aanbeveling heeft duidelijke implicaties voor patiënten, behandelaars en beleidsmakers (zie onderstaande tabel). Een aanbeveling is geen dictaat, zelfs een sterke

aanbeveling gebaseerd op bewijs van hoge kwaliteit (GRADE gradering HOOG) zal niet altijd van toepassing zijn, onder alle mogelijke omstandigheden en voor elke individuele patiënt.

Implicaties van sterke en zwakke aanbevelingen voor verschillende richtlijngebruikers		
	Sterke aanbeveling	*Zwakke (conditionele) aanbeveling*
Voor patiënten	De meeste patiënten zouden de aanbevolen interventie of aanpak kiezen en slechts een klein aantal niet.	Een aanzienlijk deel van de patiënten zouden de aanbevolen interventie of aanpak kiezen, maar veel patiënten ook niet.
Voor behandelaars	De meeste patiënten zouden de aanbevolen interventie of aanpak moeten ontvangen.	Er zijn meerdere geschikte interventies of aanpakken. De patiënt moet worden ondersteund bij de keuze voor de interventie of aanpak die het beste aansluit bij zijn of haar waarden en voorkeuren.
Voor beleidsmakers	De aanbevolen interventie of aanpak kan worden gezien als standaardbeleid.	Beleidsbepaling vereist uitvoerige discussie met betrokkenheid van veel stakeholders. Er is een grotere kans op lokale beleidsverschillen.

Organisatie van zorg

In de knelpuntenanalyse en bij de ontwikkeling van de richtlijnmodule is expliciet aandacht geweest voor de organisatie van zorg: alle aspecten die randvoorwaardelijk zijn voor het verlenen van zorg (zoals coördinatie, communicatie, (financiële) middelen, mankracht en infrastructuur). Randvoorwaarden die relevant zijn voor het beantwoorden van deze specifieke uitgangsvraag zijn genoemd bij de overwegingen. Meer algemene, overkoepelende, of bijkomende aspecten van de organisatie van zorg worden behandeld in de module Organisatie van zorg.

Commentaar- en autorisatiefase

De conceptrichtlijnmodule werd aan de betrokken (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd ter commentaar. De commentaren werden verzameld en besproken met de werkgroep. Naar aanleiding van de commentaren werd de conceptrichtlijnmodule aangepast en definitief vastgesteld door de werkgroep. De definitieve richtlijnmodule werd aan de deelnemende (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd voor autorisatie en door hen geautoriseerd dan wel geaccordeerd.

Literatuur

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Module 1 Behandeling van T1b niertumoren

Uitgangsvraag
Welke behandeling (partiële nefrectomie, totale nefrectomie, stereotactic ablative body radiotherapy (SABR), percutane ablatie) kan het beste worden toegepast bij patiënten met een niet-gemetastaseerd niercelcarcinoom tussen 4-7 cm (T1b)?

Inleiding
Gelokaliseerde niertumoren tussen 4-7 cm (T1b) worden regelmatig behandeld door middel van totale nefrectomie. De ontwikkelingen betreffende deze niertumoren laten zien dat partiële nefrectomie (niersparende operatie) ook mogelijk is. Tevens is de vraag of percutane ablatie of SABR ook mogelijke behandelingen zijn bij deze tumoren. In de huidige situatie is niersparende behandeling voor tumoren <4 cm (T1a) de richtlijn. Voor tumoren >4 cm moet niersparende behandeling overwogen worden. Met de toenemende centralisatie van behandeling van niertumoren is vaker niersparende behandeling uitvoerbaar. Wat is dan de beste techniek daarvoor?

Search and select
A systematic review of the literature was performed to answer the following 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 (T1b)?

PICO 1a: partial vs radical nephrectomy
P: Patients with a cT1b non-metastatic renal cell carcinoma
I: Partial nephrectomy
C: Radical nephrectomy
O: Survival, disease-free survival, time to recurrence, complications, quality of life, renal function

PICO 1b: (Percutaneous) ablative techniques vs (partial) nephrectomy
P: Patients with a cT1b non-metastatic renal cell carcinoma
I: Percutaneous treatment or SABR (stereotactic ablative body radiotherapy)
C: Partial or radical nephrectomy
O: Survival, disease-free survival, time to recurrence, complications, quality of life, renal function

<u>Relevant outcome measures</u>
The guideline development group considered survival and disease-free survival as critical outcome measures for decision making; and time to recurrence, complications, quality of life and renal function as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The GRADE-standard limit of 25% difference for dichotomous outcomes (RR < 0.8 or > 1.25) and 0.5 SD for continuous outcomes was taken as minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until February, 10th 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 106 hits. Studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICOs
- The intervention had to be as defined in the PICOs
- Research type: systematic review or randomized-controlled trial
- Articles written in English or Dutch

Twenty-nine studies were initially selected based on title and abstract screening. After reading the full text, 25 studies were excluded (see the table with reasons for exclusion under the tab Methods), and four studies were included (three studies for PICO 1a and one study for PICO 1b).

PICO 1a: partial vs radical nephrectomy

Results

One systematic review and two observational studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Jiang (2019) performed a systematic review and meta-analysis to compare long-term oncological outcomes in patients with 4 to 7 cm renal cell carcinoma treated with partial nephrectomy and radical nephrectomy. PUBMED, EMBASE and the Cochrane Central Register were searched for studies which were published in English dating from March 1998 to March 2018. Inclusion criteria were comparative partial nephrectomy or nephron-sparing-surgery and radical nephrectomy for the treatment of 4 to 7 cm renal tumors and evaluation of at least one oncological result such as recurrence-free survival, cancer-special survival, and overall survival. Case reports, reviews and articles without applicable data were excluded. Other exclusion criteria were studies that included both T1b and T2 or renal tumors larger than 7 cm and studies that were not comparative in nature. In total, 16 retrospective studies were included. Meta-analyses were presented for the 5- and 10-year overall survival, the 5- and 10-year cancer-special survival, the 5- and 10-year recurrence-free survival, tumor recurrence, postoperative complications and declined eGFR.

Chong (2018) compared overall survival and unplanned hospital readmissions within 30 days between partial nephrectomy and radical nephrectomy for clinically localized T1 renal tumors by analyzing the National Cancer Database between 2004 and 2013. Exclusion criteria were patients with clinical T2-4, N1, or M1 renal cell carcinoma, missing clinical stage data, renal tumors excised bilaterally or a horseshoe kidney, receiving additional treatment and concurrent or prior cancer diagnosis. Inverse probability of treatment weighting (IPTW) was performed, and therefore patients with missing data on baseline characteristics, survival, or readmission were excluded. In total, 12,656 patients underwent radical nephrectomy, and 4,419 patients underwent partial nephrectomy. The median follow-up was 44.5 months (IQR 25.7 to 68.1 months). Overall survival (months from diagnosis) was the primary outcome measure.

Venkatramani (2018) compared the overall survival and perioperative outcomes in patients with cT1b and cT2 renal cell carcinoma undergoing partial nephrectomy with those

undergoing radical nephrectomy by analyzing the National Cancer Data Base (NCDB) registry data from 2004 to 2013. Patients diagnosed with renal cell carcinoma with clinical stage cT1b-T2N0M0 were included. Exclusion criteria were patients diagnosed at death or autopsy and those with missing or unknown data for clinical TNM stage. A 1:1 propensity score matching was performed for the likelihood of receiving partial nephrectomy resulting in a total of 5,534 patients with cT1b tumor that underwent partial nephrectomy and 5,534 patients receiving radical nephrectomy. The median follow-up was 35.6 months (22.2 to 54.1 months) for partial nephrectomy and 45.1 months (26.2 to 65.7 months) for radial nephrectomy. Overall survival was the primary outcome measure.

Results

Survival

Jiang (2019) reported the 5- and 10-year overall survival. At 5-years, no significant difference was found in overall survival between patients who underwent partial nephrectomy and radical nephrectomy (RR 1.02, 95% CI 1.00 to 1.05, p=0.05) (Figure 1.1). The overall survival at 10-years was also not significantly different between patients who underwent partial nephrectomy and radical nephrectomy (RR 1.17, 95% CI 0.95 to 1.44) (Figure 1.2).

Chong (2018) reported that partial nephrectomy is associated with improved overall survival as compared to radical nephrectomy (HR = 0.89, 95% CI 0.82 to 0.99, p=0.025), according to the IPTW-adjusted Cox proportional hazards regression. However, no significant difference was found when applying a more robust sandwich-type variance estimator (HR = 0.89, 95% CI 0.79 to 1.02, p =0.106). In addition, the 5-year IPTW-adjusted Kaplan-Meier (IPTW-KM) was 85.3% for partial nephrectomy and 84.3% for radical nephrectomy, while the 10-year IPTW-KM was 70.8% and 63.6%, respectively.

Venkatramani (2018) reported that partial nephrectomy is associated with a significantly better overall survival than radical nephrectomy (HR=0.81, 95% CI 0.73 to 0.90, p<0.001) on multivariate analyses.

Figure 1.1. 5-year overall survival, comparison between partial nephrectomy (PN) and radical nephrectomy (RN). Adapted from Jiang 2019.

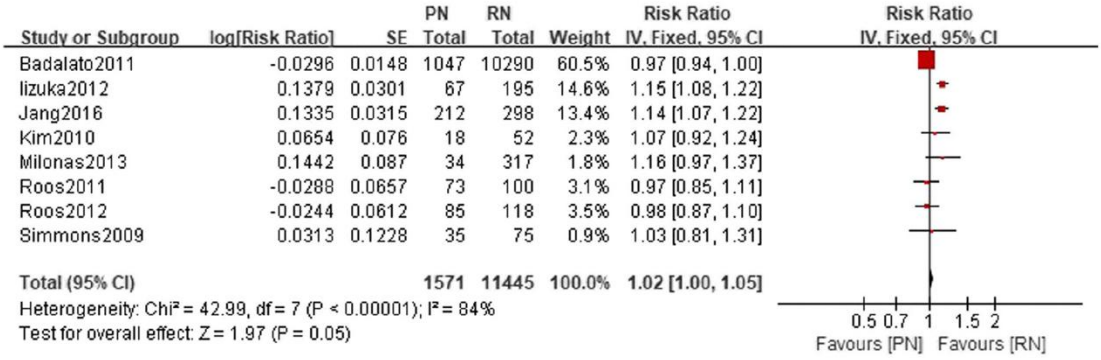
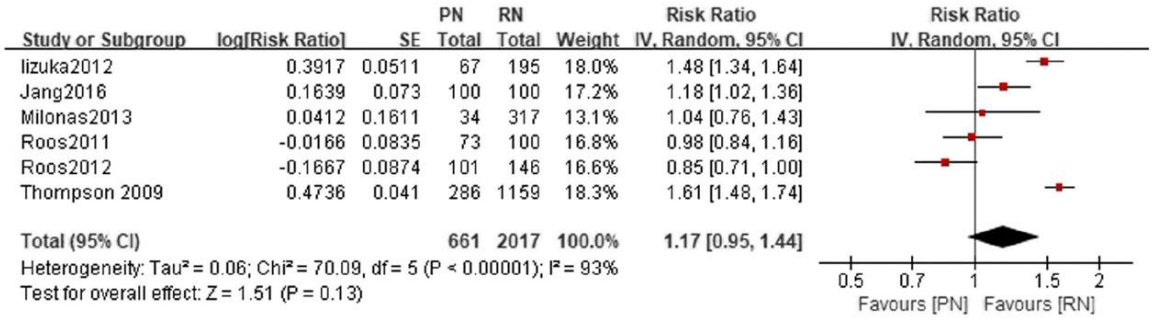


Figure 1.2. 10-year overall survival, comparison between partial nephrectomy (PN) and radical nephrectomy (RN). Adapted from Jiang 2019.



Disease-free survival

Jiang (2019) reported the recurrence-free survival after 5- and 10-years. No significant difference in recurrence-free survival was found between patients undergoing partial nephrectomy and radical nephrectomy at 5-years (RR 0.99, 95% CI 0.98 to 1.01, p=0.20) (Figure 2.1). At 10-years, the recurrence-free survival was similar for patients who underwent partial nephrectomy and radical nephrectomy (RR 1.00, 95% CI 0.91 to 1.10) (Figure 2.2).

Figure 2.1. 5-year recurrence-free survival, comparison between partial nephrectomy (PN) and radical nephrectomy (RN). Adapted from Jiang 2019.

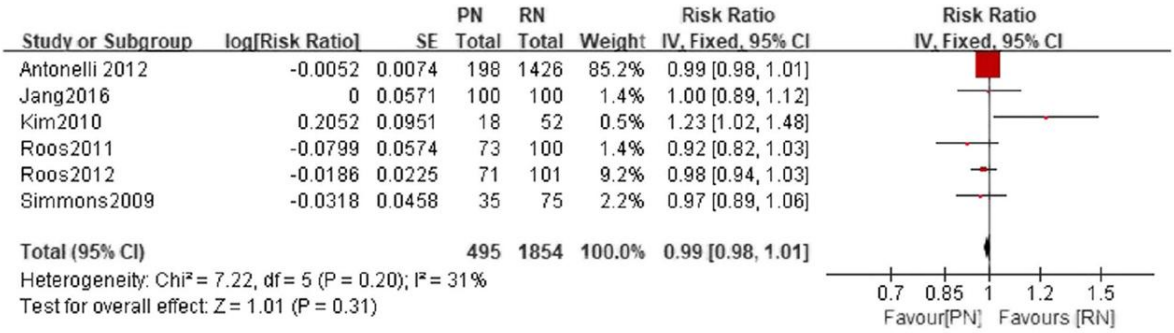
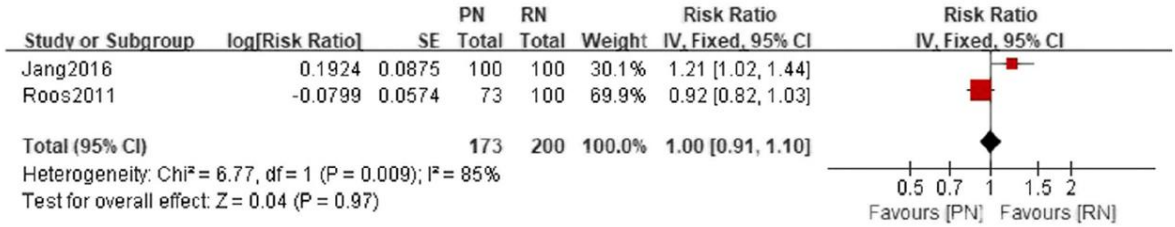


Figure 2.2. 10-year recurrence-free survival, comparison between partial nephrectomy (PN) and radical



nephrectomy (RN). Adapted from Jiang 2019.

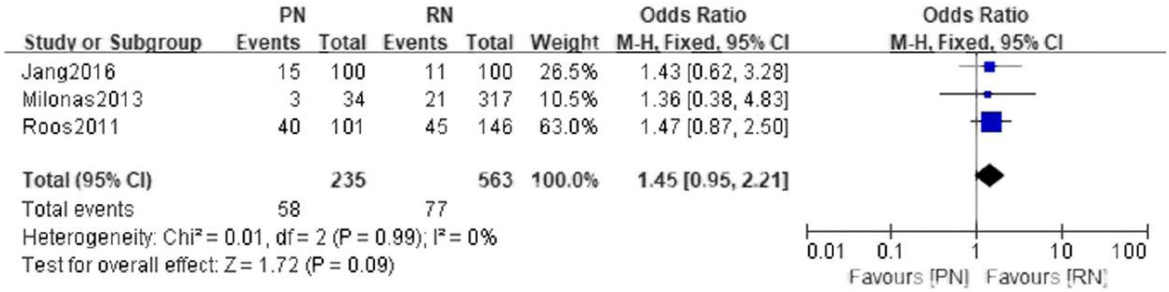
Time to recurrence

Not reported.

Complications

Jiang (2019) reported post-operative complications. No difference in complications were found between patients who underwent partial nephrectomy and radical nephrectomy (OR 1.45, 95% CI 0.95 to 2.21) (Figure 3).

Figure 3. Postoperative complications, comparison between partial nephrectomy (PN) and radical nephrectomy (RN). Adapted from Jiang 2019



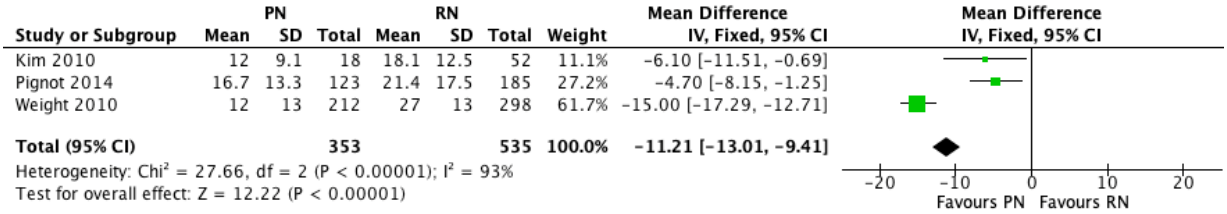
Quality of life

Not reported.

Renal function

Jiang (2019) reported declined eGFR. A significant difference in declined eGFR was found between patients who underwent partial nephrectomy and radical nephrectomy (MD -11.21, 95% CI -10.30 to -7.99) (Figure 4).

Figure 4. Declined eGFR, comparison between partial nephrectomy (PN) and radical nephrectomy (RN).



Level of evidence of the literature

According to GRADE, systematic reviews of observational studies and observational studies start at a low level of evidence.

The level of evidence regarding the outcome measure **survival** was downgraded to GRADE very low, one level for risk of bias and one level because of inconsistency.

The level of evidence regarding the outcome measure **disease-free survival** was downgraded to GRADE very low, one level because of risk of bias.

The level of evidence regarding the outcome measure **time to recurrence** could not be assessed with GRADE as this outcome measure was not studied in the included study.

The level of evidence regarding the outcome measure **complications** was downgraded to GRADE very low, one level for risk of bias and one level for imprecision.

The level of evidence regarding the outcome measure **quality of life** could not be assessed with GRADE as this outcome measure was not studied in the included study.

The level of evidence regarding the outcome measure **renal function** was downgraded to GRADE very low, one level for risk of bias, one level for inconsistency, and one level for imprecision.

Conclusions

Very low GRADE	The evidence is very uncertain about the effect of partial nephrectomy on **survival** when compared with radical nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma. *Jiang, 2019; Chong 2018; Venkatramani 2018*

Very low GRADE	The evidence is very uncertain about the effect of partial nephrectomy on **disease-free survival** when compared with radical nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma. *Jiang, 2019*

NO GRADE	No evidence was found regarding the effect of partial nephrectomy on **time to recurrence** when compared with radical nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma.

Very low GRADE	The evidence is very uncertain about the effect of partial nephrectomy on **complications** when compared with radical nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma. *Jiang, 2019*

NO GRADE	No evidence was found regarding the effect of partial nephrectomy on **quality of life** when compared with radical nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma.

Very low GRADE	The evidence is very uncertain about the effect of partial nephrectomy on **renal function** when compared with radical nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma. *Jiang, 2019*

PICO 1b: Percutaneous ablative techniques vs (partial) nephrectomy

Results

One systematic review was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Chan (2022) performed a systematic review and meta-analysis to compare oncological outcomes in patients undergoing percutaneous ablative therapies (AT) or partial nephrectomy (PN) for T1a or T1b small renal masses. Medline, EMBASE, Cochrane CENTRAL and conference proceedings were search on 15th July 2020. No date limit was applied and only articles in English or those containing an English abstract were included. All randomized controlled trials or observational studies comparing the use of AT and PN in patients with T1a or T1b small renal masses that report the outcome of interest including survival outcomes and peri-operative outcomes were included. Exclusion criteria were studies only focusing on solitary kidneys, bilateral tumors, patients with inherited RCC syndromes or studies focusing on T1 solely without stratifying results into T1a and T1b. Besides, letters, editorials, single-arm studies, pediatric studies, and non-human studies were excluded. For T1b, eight retrospective cohort studies were included. Meta-analyses were presented for overall complications, minor complications, and major complications in T1b patients.

Results

Survival

In the study of Chan (2022), six studies reported the overall survival. Most studies found overall survival to be similar in both groups, but one found worse in ablative therapy patients.

Disease-free survival

In the study of Chan (2022), two studies reported contradicting results regarding the disease-free survival.

Time to recurrence

Not reported.

Complications

Chan (2022) reported overall, minor (Clavien Dindo Grade ≤2) and major (Clavien Dindo Grade ≥3) post-operative complications. Similar overall, minor, and major complication rates among ablative therapy and partial nephrectomy patients were found (RR =0.97, 95% CI 0.63 to 1.50, p = 0.91, Figure 5.1 and 5.2; RR = 0.96, 95% CI 0.57 to 1.61, p = 0.87, Figure 6.1 and 6.2; RR = 0.69, 95% CI 0.33 to 1.44, p = 0.28, Figure 7.1 and 7.2).

Figure 5.1. Overall complications in T1b patients by approach. Adapted from Chan 2022.

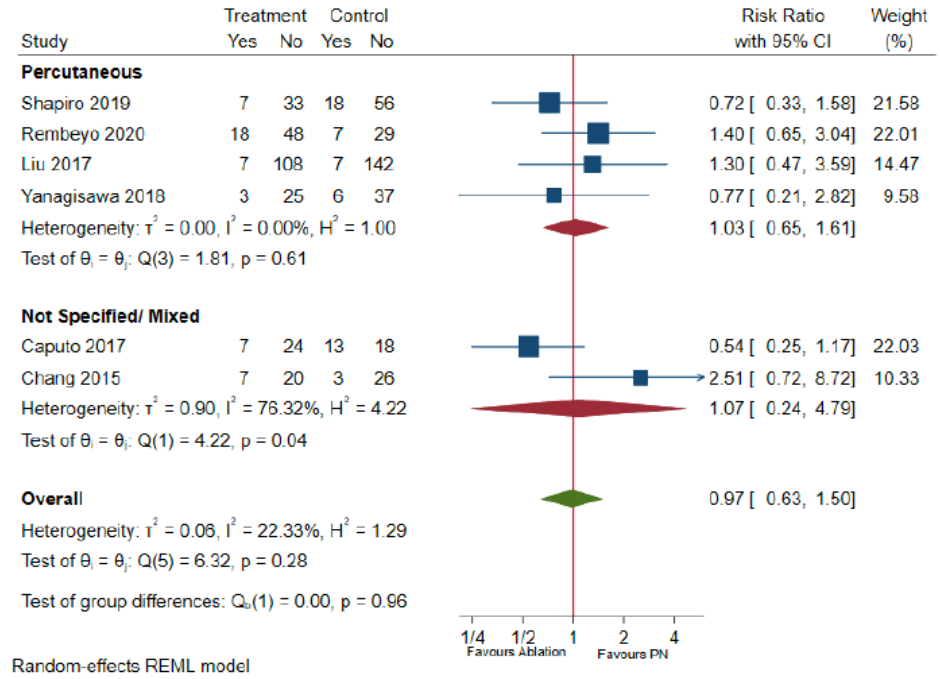
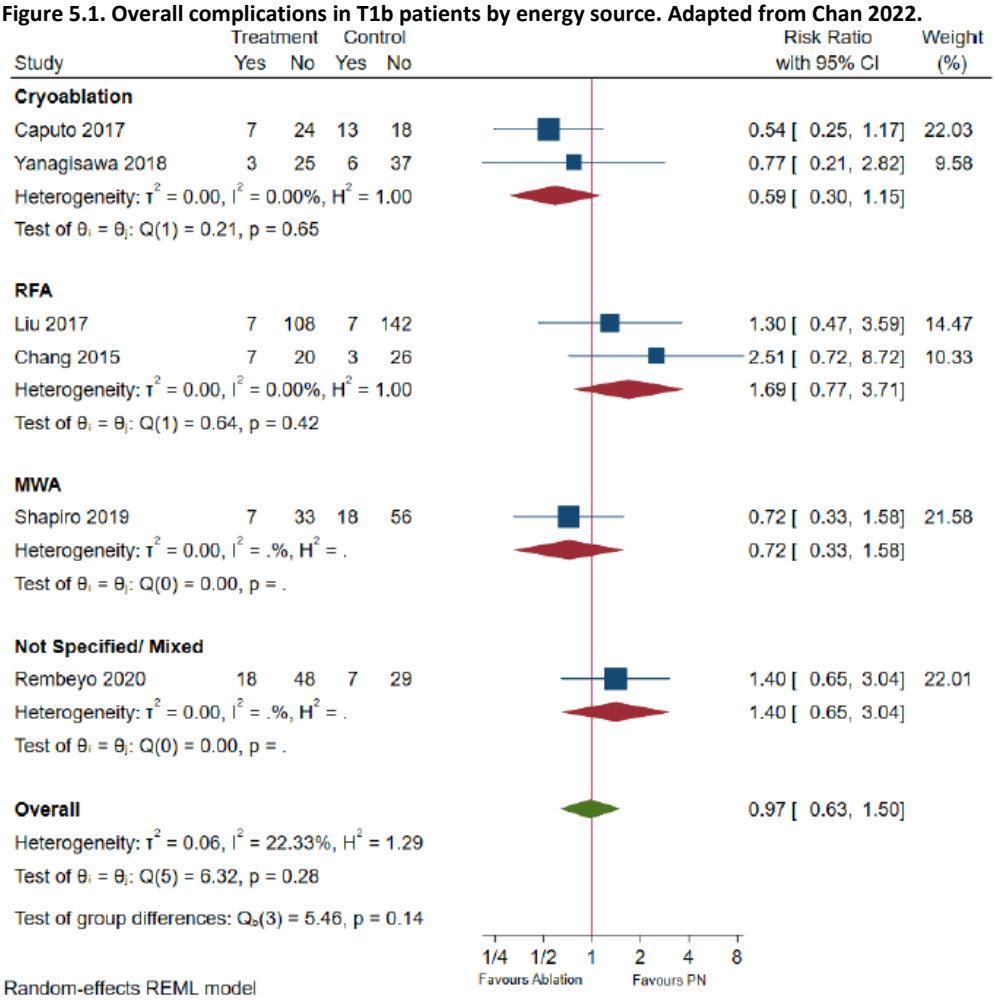


Figure 5.1. Overall complications in T1b patients by energy source. Adapted from Chan 2022.



RFA=radiofrequency ablation; MWA= microwave ablation

Figure 6.1. Minor complications (Clavien Dindo Grade ≤2) in T1b patients by approach. Adapted from Chan 2022

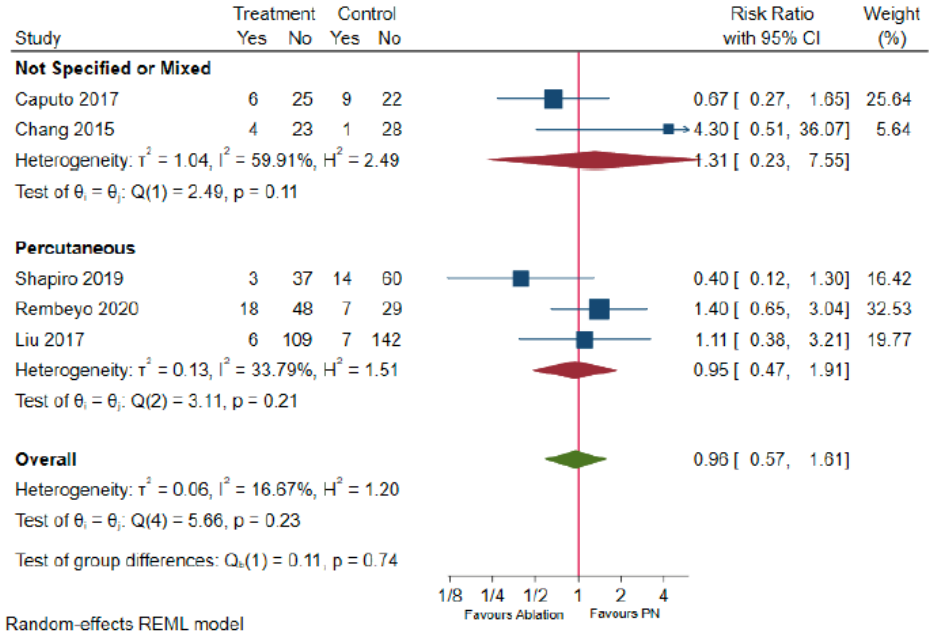
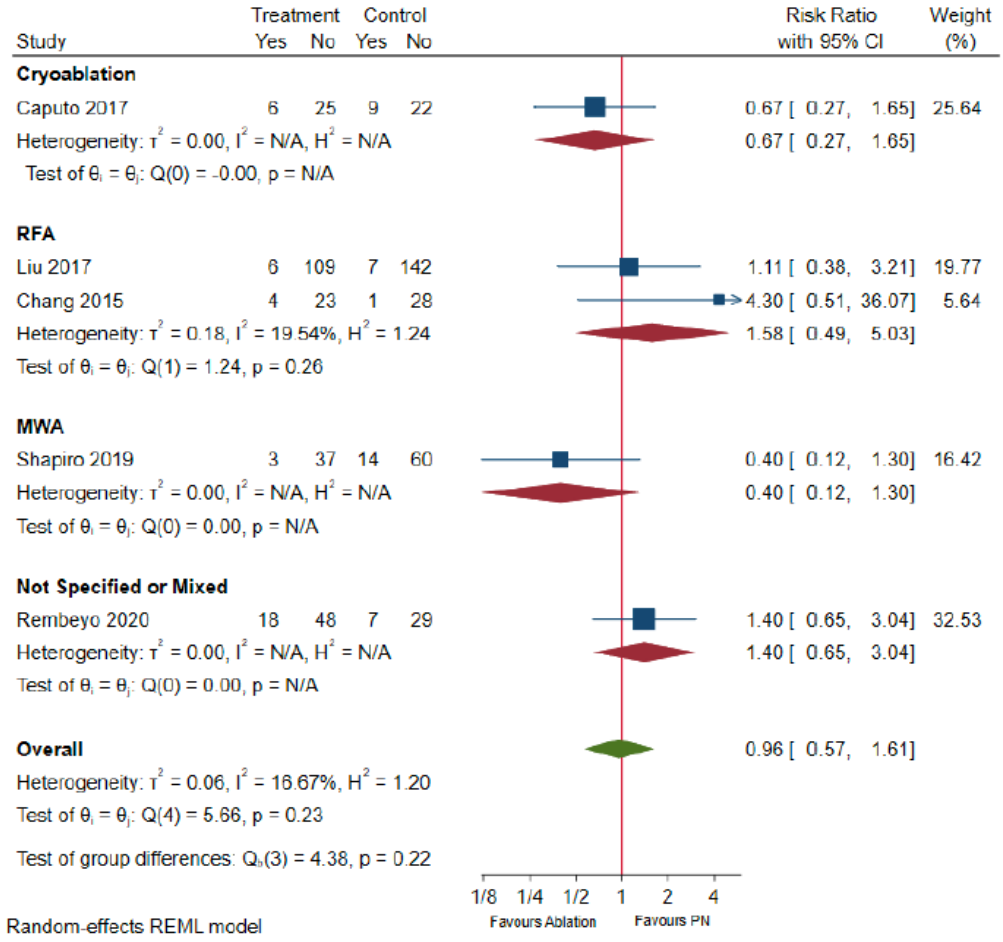


Figure 6.2. Minor complications (Clavien Dindo Grade ≤2) in T1b patients by energy source. Adapted from Chan 2022



RFA=radiofrequency ablation; MWA= microwave ablation

Figure 7.1. Major complications (Clavien Dindo Grade ≥3) in T1b patients by approach. Adapted from Chan 2022.

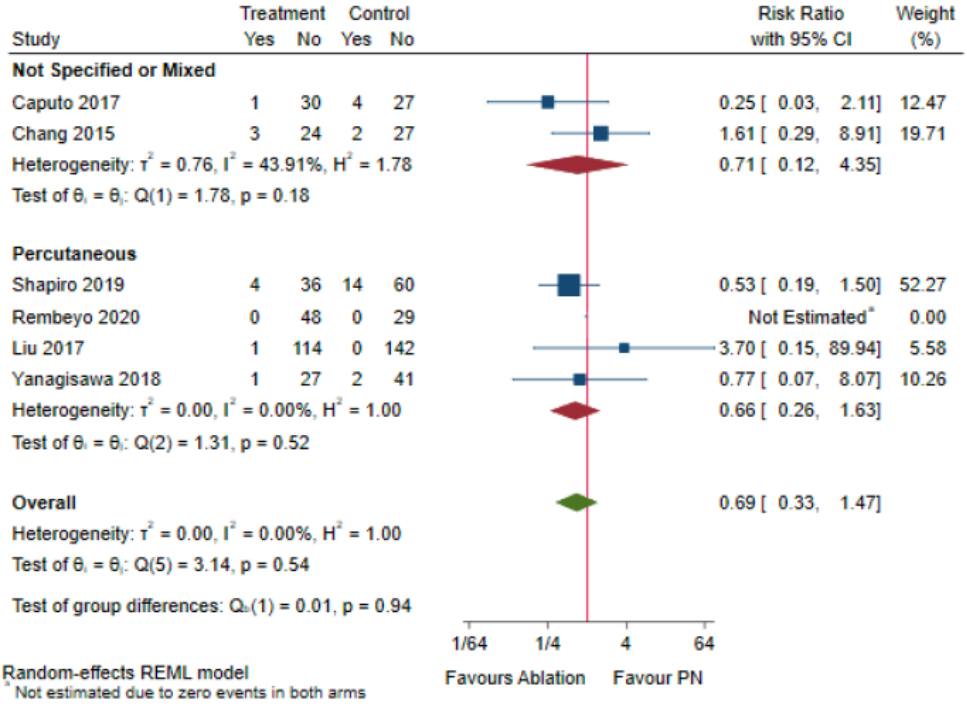
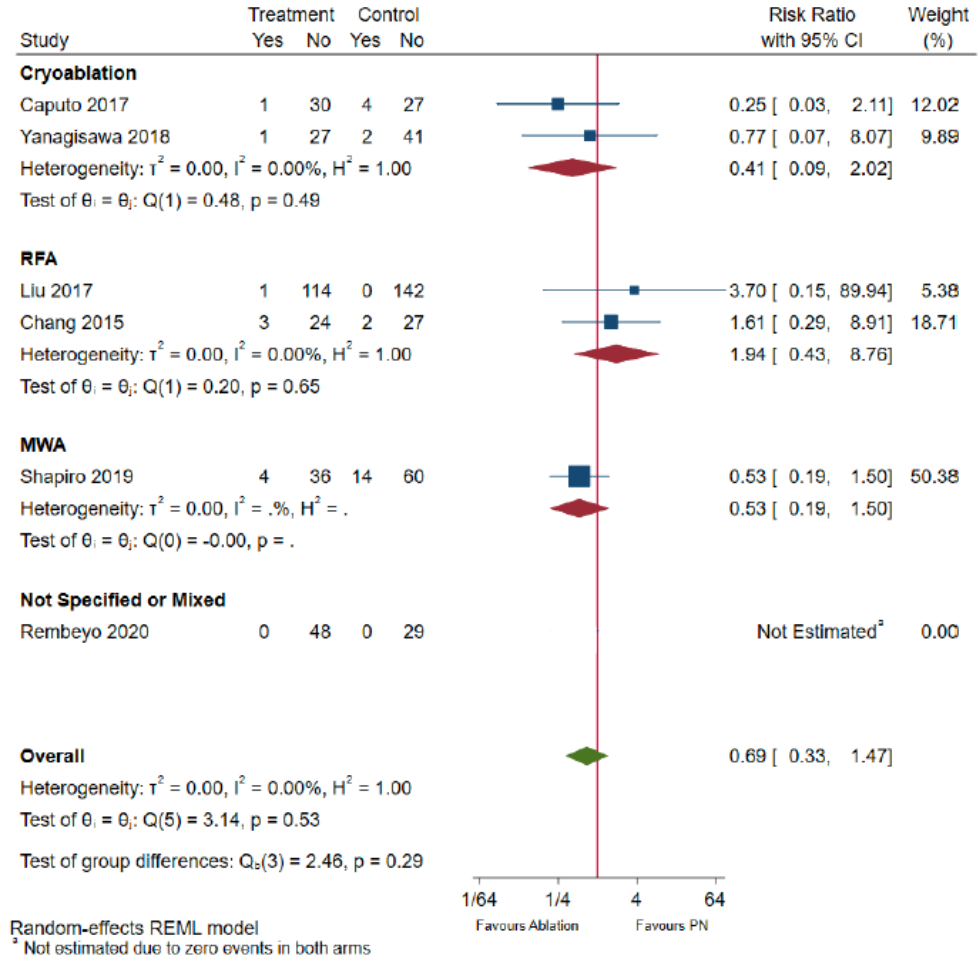


Figure 7.2. Major complications (Clavien Dindo Grade ≥3) in T1b patients by energy source. Adapted from Chan 2022.



RFA=radiofrequency ablation; MWA= microwave ablation

Quality of life

Not reported.

Renal function

In the study of Chan (2022), four studies reported contradicting results about the change in renal function post-operatively.

<u>Level of evidence of the literature</u>

According to GRADE, systematic reviews of observational studies start at a low level of evidence.

The level of evidence regarding the outcome measure **survival** was downgraded to GRADE very low by one level for risk of bias.

The level of evidence regarding the outcome measure **disease-free survival** was downgraded to GRADE very low by one level for risk of bias.

The level of evidence regarding the outcome measure **time to recurrence** could not be assessed with GRADE as this outcome measure was not studied in the included study.

The level of evidence regarding the outcome measure **complications** was downgraded to GRADE very low by one level for risk of bias and two levels for imprecision.

The level of evidence regarding the outcome measure **quality of life** could not be assessed with GRADE as this outcome measure was not studied in the included study.

The level of evidence regarding the outcome measure **renal function** was downgraded to GRADE very low by one level for risk of bias.

Conclusions

Very low GRADE	The evidence is very uncertain about the effect of percutaneous ablative therapies on **survival** when compared with partial nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma. *Chan, 2022*

Very low GRADE	The evidence is very uncertain about the effect of percutaneous ablative therapies on **disease-free survival** when compared with partial nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma. *Chan, 2022*

NO GRADE	No evidence was found regarding the effect of percutaneous ablative therapies on **time to recurrence** when compared with partial nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma.

Very low GRADE	The evidence is very uncertain about the effect of percutaneous ablative therapies on **complications** when compared with partial nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma. *Chan, 2022*

NO GRADE	No evidence was found regarding the effect of partial nephrectomy on **quality of life** when compared with partial nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma.

Very low GRADE	The evidence is very uncertain about the effect of percutaneous ablative therapies on **renal function** when compared with partial nephrectomy in patients with a cT1b non-metastatic renal cell carcinoma. *Chan, 2022*

Overwegingen – van bewijs naar aanbeveling

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>

De werkgroep heeft een literatuurstudie verricht naar de (on)gunstige effecten van partiële nefrectomie, totale nefrectomie, SABR en percutane ablatie bij patiënten met een niet-gemetastaseerd niercelcarcinoom tussen 4-7 cm (T1b).

PICO 1a: partiële vs totale nefrectomie

Helaas blijken er maar een paar bruikbare publicaties te zijn om de vraag te beantwoorden of een partiële nefrectomie bij T1b tumoren te verkiezen is boven een radicale nefrectomie. Veel studies zijn niet gerandomiseerd, gaan meer over technische verschillen in de partiële nefrectomie, en zijn niet vergelijkend met nefrectomie. Op basis van de resultaten van de literatuuranalyse lijken er geen verschillen te zijn tussen partiële nefrectomie en totale nefrectomie voor de cruciale uitkomstmaten overleving en ziektevrije overleving en de belangrijke uitkomstmaten complicaties en nierfunctie. De bewijskracht werd beoordeeld als zeer laag vanwege imprecisie, inconsistentie en risico op bias. De studie van Jiang laat een duidelijk voordeel in nierfunctiebehoud zien voor de partiële nefrectomie vergeleken met een nefrectomie, maar er zijn geen andere studies die hiernaar hebben gekeken: mogelijk omdat het zo evident is dat bij niersparend opereren er minder nierfunctieverlies is dan bij een nefrectomie. Opvallend is dat de kans op complicaties in de studie van Jiang niet verschilt voor partiële of radicale nefrectomie. Dit kan berusten op een selectiebias: keuze voor partiële nefrectomie vooral bij jongere, fittere patiënten. Er werd geen literatuur gevonden voor het verschil tussen partiële en totale nefrectomie voor de belangrijke uitkomstmaten tijd tot recidief en kwaliteit van leven.

Samenvattend kunnen op grond van de gevonden beperkte literatuur geen conclusies getrokken worden met een hogere gradering dan “zeer laag “ over de keuze tussen een partiële nefrectomie of een radicale nefrectomie bij T1b tumoren.

Naar de mening van de werkgroepleden is het verantwoord om een partiële nefrectomie bij T1b tumoren te overwegen mits dit technisch uitvoerbaar en oncologisch veilig is.

PICO 1b: (percutane) ablative techniques vs (partiële) nefrectomie

Op basis van de resultaten van de literatuuranalyse lijken er geen verschillen te zijn tussen (percutane) ablatieve therapieën en (partiële) nefrectomie voor de cruciale uitkomstmaten overleving en ziektevrije overleving en de belangrijke uitkomstmaten complicaties en nierfunctie. De bewijskracht werd beoordeeld als zeer laag vanwege risk of bias. Bij alle vergelijkende studies die percutane ablatie vergelijken met partiële nefrectomie of nefrectomie is sprake van een bias: patiënten die geopereerd worden zijn over het algemeen jonger en hebben minder comorbiditeit. Er werden geen studies gevonden die SABR vergelijken met partiële nefrectomie. Er werd geen literatuur gevonden voor het verschil tussen percutane ablatieve therapieën en partiële nefrectomie voor de belangrijke uitkomstmaten tijd tot recidief en kwaliteit van leven.

Studies over recidiefkans en overleving van percutane ablatieve technieken bij T1b niercelcarcinoom zijn zeldzaam, en zijn niet vergelijkend. De meeste technieken zijn ontwikkeld voor kleinere niertumoren en hebben een maximale grootte van een tumor waarvoor ze kunnen worden toegepast. Voor een aantal technieken in de praktijk tot 4-5 cm. Toepassing bij T1b tumoren tot 7 cm kan betekenen dat meerdere sessies nodig zijn om locale controle te verkrijgen.

In de huidige praktijk lijkt de grootte of locatie van de tumor voor wat betreft het verkrijgen van lokale controle van de tumor middels SABR geen beperking te zijn. De fractionering van SABR (1-5 fracties) hangt af van tumorgrootte en nabijgelegen radiosensitieve organen. Routinematige biopten na SABR worden niet aanbevolen, omdat positieve resultaten niet voorspellend zijn voor tumorprogressie en de tumor door de behandeling veranderingen ondergaat, zoals verminderde cellulaire activiteit en verhoogde fibrose. Beeldvorming met CT wordt gebruikt om de respons te beoordelen, waarbij veranderingen in tumorgrootte en contrastversterking over een langere periode worden

gevolgd. Hoewel contrastversterking na SABR langzaam kan afnemen, kan deze aanvankelijk ook toenemen door inflammatoire effecten op de bloedvaten. De RECIST-criteria worden momenteel gebruikt voor responsbeoordeling, maar houden geen rekening met post-SABR veranderingen zoals necrose en senescentie, wat de interpretatie uitdagender maakt (Siva Lancet Oncol 2024).
Er werden enkele niet vergelijkende studies gevonden over SABR. Recent beschrijft Rich, 2022) in een overzichtsartikel de behandeling van T1a -T2 niertumoren met SABR. Het betreft meestal kleine series, met (partiële) nefrectomie. De ervaringen die hierin worden beschreven, met korte follow-up, zijn gunstig, met goede lokale controle en beperkte toxiciteit. De resultaten van de recent gepubliceerde fase II FASTRACK studie in 70 patienten bevestigen dit (Siva, 2024).

Recent werd in een systematic review en meta-analyse vergelijkende effectiviteit en veiligheid van ablatiebehandelingen bij de behandeling van primair gelokaliseerd niercelcarcinoom ge-evalueerd. Voor grotere tumoren (≥4 cm) had SABR na 5 jaar de hoogste lokale controle: 93% (85–98%), RFA en MWA waren minder effectief: respectievelijk 79% en 82% en cryoablatie liet een betere lokale controle zien dan RFA of MWA: 85%. Het effect op de nierfunctie na 5 jaar was vergelijkbaar tussen SABR, RFA en cryoablatie, met een afname tussen de 10 – 13 ml/min per 1.73 m^2, voor MWA was er geen data hierover. Er was geen specifieke data over graad 3-4 bijwerkingen voor tumoren ≥4 cm, wel dat grotere tumoren een verhoogde behandelingsgerelateerde toxiciteit hebben ten opzichte van tumoren onder de 4 cm waar dit tussen de 1-3% ligt (Huang, 2025).

Net als bij T1a tumoren lijkt het de werkgroep wenselijk om patiënten met cT1b niertumoren prospectief te registreren in een landelijke database waarbij tevens de RENAL score wordt vastgelegd zodat in de toekomst beter de voor- en nadelen van de behandelopties in de Nederlandse setting gewogen kunnen worden. Alhoewel er geen complexiteitsscore superieur is in vergelijking met de andere scores is de werkgroep van mening dat de RENAL score door de eenvoud en toepasbaarheid de voorkeur heeft. Dit vergt overeenstemming en inzet van de diverse betrokken disciplines.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
De werkgroep heeft op grond van de beschikbare literatuur geen verschil kunnen vinden tussen de diverse behandelingen voor de cruciale uitkomstmaten overleving en ziektevrije overleving en de belangrijke uitkomstmaten complicaties en nierfunctie.
Het postoperatieve herstel van patiënten na percutane technieken verloopt in het algemeen vlotter dan na een partiële nefrectomie. De opnameduur voor een partiële nefrectomie is langer dan voor ablatieve technieken. Percutane ablatie dient daarom bij oudere patiënten met meer comorbiditeit als alternatief voor een partiële nefrectomie besproken te worden. Hetzelfde geldt voor patiënten waarbij een partiële nefrectomie op grond van eerdere chirurgie als veel gecompliceerder wordt ingeschat. In deze situatie kan zeker ook SABR als alternatief worden overwogen, een niet-invasieve behandeling in 1-5 sessies..

<u>Kosten (middelenbeslag)</u>
De kosten effecten van percutane ablatieve technieken en partiële nefrectomie zijn niet goed onderzocht. Door de kortere opnameduur of door het ontbreken van een noodzakelijke opname (SABR) kunnen percutane ablatie technieken of SABR goedkoper zijn. Yeaman (2022) toont voor behandeling van T1a tumoren in de USA aan dat microwave ablatie voordeliger is dan partiële nefrectomie. Dit voordeel kan verdwijnen wanneer bij T1b tumoren meerdere ablatieve behandelingen/opnamen nodig zijn, omdat de tumor groter is. Kumar,

2021 benoemt de prijs van SABR (12 242 Amerikaanse dollar) in de United States of America (USA). Er is een grote range in de prijs van een partiële nefrectomie (13 000 – 18 000 Amerikaanse dollar, USA). (Buse, 2018)
In een aantal gevallen is op grond van biopten vooraf of tijdens ablatie toch geen zekerheid te verkrijgen over het al dan niet goedaardig zijn van de afwijking. Dit kan betekenen dat bij een aantal patiënten geen duidelijkheid wordt verkregen over de aard van de tumor, bij niet gediagnosticeerde benigne tumoren wordt toch de reguliere follow up gevolgd. Bij (partiële) nefectomie speelt dit laatste niet doordat definitieve zekerheid over de aard van de tumor verkregen is.

Aanvaardbaarheid, haalbaarheid en implementatie
Er zijn in Nederland ziekenhuizen waar ervaring is met het uitvoeren van partiele nefrectomie en alternatieve technieken (percutane ablatie / SABR). Ziekenhuizen die niet over deze ervaring of mogelijkheden beschikken dienen patienten met T1b niertumoren te bespreken. Door patiënten te bespreken vindt er verspreiding van kennis plaats en wordt er meer naar eenduidig beleid gestreefd.

Aanbeveling(en)
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
De keuze tussen partiële nefrectomie , de verschillende percutane ablatieve technieken zoals RFA, MWA, cryoablatie en SABR of radicale nefrectomie dient te worden gemaakt op basis van tumor karakteristieken (zoals tumorgrootte, lokalisatie van de tumor), patiënt karakteristieken (zoals leeftijd, levensverwachting, comorbiditeit, eerdere chirurgie), en voorkeur van de patiënt (zekerheid over aard van de tumor, sneller herstel)

Overweeg bij cT1b niertumoren nefronsparende behandeling.

Gebruik RENAL nephrometry score bij bepalen van de behandelstrategie en registreer deze in het radiologie verslag en de conclusie van het multidisciplinair overleg. Bepaal het behandeladvies in een multidisciplinair overleg en registreer de conclusie en overwegingen.

Kennislacunes
Het literatuuronderzoek voor de onderzoeksvraag welke therapie de beste is voor de behandeling van T1b niertumoren was gericht op operatie, (percutane) ablatieve technieken zoals RFA, MWA, cryoablatie en SABR . Goede vergelijkende studies zijn zeer schaars.
Samengevat blijkt dat geen van de behandelstrategieën eenduidig betere uitkomsten geeft omdat alle conclusies na interpretatie van de gevonden literatuur gegradeerd worden als laag of zeer laag.
De conclusie die wel getrokken kan worden is dat er een kennislacune bestaat met betrekking tot de vraag welke behandeling het beste is bij cT1b niertumoren. Het lijkt de werkgroep hierom wenselijk om in ieder geval patiënten met cT1b niertumoren prospectief te registreren in een landelijke database waarbij tevens de RENAL score wordt vastgelegd zodat in de toekomst beter de voor- en nadelen van de behandelopties in de Nederlandse setting gewogen kunnen worden. Daarnaast is er dringende behoefte aan een vergelijkend gerandomiseerd onderzoek waarbij gedacht wordt aan vier behandelarmen en partiële nefrectomie wordt uitgezet tegen een ablatieve techniek, radicale nefrectomie en SABR. Alhoewel er geen complexiteitsscore superieur is in vergelijking met de andere scores is de werkgroep van mening dat de RENAL score door de eenvoud en toepasbaarheid de voorkeur heeft. Dit vergt overeenstemming en inzet van de diverse betrokken disciplines.

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Module 2 Keuze eerstelijns systemische therapie heldercellig niercelcarcinoom

Uitgangsvraag
Welke eerstelijns systeemtherapie heeft de voorkeur bij patiënten met gemetastaseerd heldercellig niercelcarcinoom?

Introduction
In recent years, the options for systemic treatment of patients with metastatic renal cancer have rapidly expanded. Great improvements have been made with the advent of immune-therapy and the combination with targeted agents. This has raised the important question how these therapeutic modalities are optimally used to benefit patients. Sequencing of these therapies may be key to improve disease control, quality of live and survival.

Search and select
A systematic review of the literature was performed to answer the following question:

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

Relevant outcome measures
The guideline development group considered progression-free survival and overall survival as a critical outcome measure for decision making; and Quality of Life and treatment-related adverse events as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a relative risk (RR) or hazard ratio (HR) < 0.80 or >1.25 as a minimal clinically (patient) important difference for dichotomous or survival variables, and >0.5 SD for continuous variables.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched using relevant search terms until July 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 521 hits. Studies were selected based on the following criteria Systematic reviews or randomized clinical trials comparing various combinations of immunotherapy and targeted therapy with each other or with sunitinib in patients with metastatic clear cell renal carcinoma. 38 studies were initially selected based on title and abstract screening. After reading the full text, 37 studies were excluded (see the table with reasons for exclusion under the tab Methods), and one systematic review and network meta-analysis (NMA) was included. At the time of the search only a protocol for this SR was available, but the full SR with NMA was published in May 2023 and included in this summary in August 2023.

Results
One SR with NMA was included in the analysis of the literature. Important study characteristics and results of the included RCTs with relevant comparisons are summarized

in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table. Risk of bias assessment of the individual RCTs is copied from Aldin (2023).

Summary of literature

Description of studies

One Cochrane SR with NMA was included (Aldin, 2023), which included 36 RCTs comparing two treatments (targeted therapy or immunotherapy) among patients with previously untreated mRCC. The comprehensive search was performed in February 2022, and information was retrieved from the Clinical Study Reports as much as possible. Data extraction and assessment of Risk of Bias was performed by two reviewers independently, and the SR was reported in a clear and comprehensive way. The SR included 36 RCTs, in 16 of which sunitinib was used as comparator. In one RCT the outcomes considered critical or important by the guideline development group were not reported for all risk groups combined, but only for subgroups with intermediate or poor risk (NCT02684006, JAVELIN renal 101, Haanen, 2021).

Results

Since there were no 'closed loops' in the network but only pairwise comparisons with sunitinib, the results of the network meta-analysis were ignored. The data for the one-to one comparisons were copied from the forest plots of pairwise comparisons (all risk groups combined and intermediate and poor risk groups according to the International Metastatic RCC Database Consortium (IMDC))(Aldin, 2023). Results were not pooled, as the trials were considered insufficiently comparable with regards to study populations and interventions. The results for progression-free survival in all risk groups combined and in IMDC intermediate and poor risk groups are shown in Tables 1 and 2, respectively. The results for overall survival in all risk groups combined and in IMDC intermediate and poor risk groups are shown in Tables 3 and 4, respectively. Results for SAEs in all risk groups combined are shown in Table 5.

Progression-free survival - all risk groups combined

The outcome PFS was reported for all risk groups combined in 15 RCTs (Table 1), of which only one was considered to have a low risk of bias (trial number NCT00720941, COMPARZ). The effect estimator of this trial, comparing pazopanib with sunitinib (HR [95% CI] 1.05 [0.90, 1.22]) was not clinically relevant. Clinically relevant effects in favour of the intervention were reported for lenvantinib + pembrolizumab (HR [95% CI] 0.39 [0.32, 0.48]), pembrolizumab + axitinib (HR [95% CI] 0.68 [0.58, 0.80]), nivolumab + cabozantinib (HR [95% CI] 0.51 [0.41, 0.64], cabozantinib (HR [95% CI] 0.48 [0.31, 0.74](some concerns for RoB), lenvantinib + everolimus (HR [95% CI] 0.65 [0.53, 0.80]), but these trials were at high risk of bias.

Progression-free survival – IMDC intermediate and poor risk groups

The outcome PFS was reported for IMDC intermediate and poor risk groups in five RCTs (Table 2). All five trials reported clinically relevant effects in favour of the intervention, but all but one were considered to have a high risk of bias. The one trial with some concerns for RoB (trial number NCT01835158 (CABOSUN)) reported HR [95% CI] of 0.52 [0.32, 0.83] and 0.31 [0.11, 0.90] for IMDC intermediate and poor risk groups, respectively.

Overall survival – all risk groups combined

The outcome OS (Table 3) was reported for all risk groups combined in 13 RCTs. The results of the low risk of bias RCTs indicate a clinically relevant effect compared to sunitinib of nivolumab + ipilimumab (HR [95% CI] 0.69 [0.59, 0.81]) and of pembrolizumab + axitinib (HR [95% CI] 0.73 [0.60, 0.88]). The effect estimators of the other two trials with low risk of bias

are not clinically relevant: pazopanib (HR [95% CI] 0.92 [0.79, 1.07]) and atezolizumab + bevacizumab (HR [95% CI] 0.91 [0.76, 1.08]). In two other trials a clinically relevant effect in favour of the intervention was reported (lenvantinib + pembrolizumab, HR [95% CI] 0.66 [0.49, 0.88], nivolumab + cabozantinib, HR [95% CI] 0.60 [0.44, 0.82]), but these trials had a high risk of bias.

Overall survival - IMDC intermediate and poor risk groups

The outcome PFS was reported for IMDC intermediate and poor risk groups in six RCTs (Table 4), of which only one was considered to have a low RoB (NCT02231749 (Checkmate 214)). The effect estimator of this trial (HR [95% CI] 0.65 [0.54, 0.78]) for IMDC intermediate-poor risk groups was clinically relevant in favour of nivolumab + ipilimumab. Clinically relevant effects in favour of the intervention were reported for avelumab + axitinib in the IMDC poor risk group (HR [95% CI] 0.60 [0.40, 0.91]), and for lenvantinib and pembrolizumab in the IMDC intermediate and poor risk groups (HR [95% CI] 0.72 [0.50, 1.04] and 0.30 [0.14, 0.64], respectively), but these trials were at high risk of bias.

Quality of Life – all risk groups combined

The only intervention for which Aldin (2023) could report the outcome quality of life was pazopanib (trial number NCT00720941, COMPARZ). The mean difference on the FACIT-F (Functional Assessment of Chronic Illness Therapy Fatigue, range 0 to 52) at the end of treatment was 9.00 (95% CI -9.86, 27.86) in favour of pazopanib. However, this information was only available for four trial participants, two in each trial arm. The trial was considered to have a high risk of bias for this outcome.

The outcome Quality of Life was not reported for the IMDC intermediate and poor risk groups separately.

Table 1. Progression-free survival. Results of pairwise comparisons with sunitinib (all risk groups combined)

Intervention	RCT number (name)	Risk of Bias*	Progression-free survival HR [95% CI]	Clinically relevant in favour of
Lenvantinib + Pembrolizumab	NCT02811861a (CLEAR)	High (D3, 4)	0.39 [0.32, 0.48]	Lenvantinib + Pembrolizumab
Nivolumab + Ipilimumab	NCT02231749 (Checkmate 214)	High (D4)	0.89 [0.76, 1.05]	-
Pembrolizumab + Axitinib	NCT02853331 (KEYNOTE-426)	High (D5)	0.68 [0.58, 0.80]	Pembrolizumab + Axitinib
Nivolumab + Cabozantinib	NCT03141177 (CHECKMATE 9ER)	High (D3, 5)	0.51 [0.41, 0.64]	Nivolumab + Cabozantinib
Cabozantinib	NCT01835158 (CABOSUN)	Some concerns (D5)	0.48 [0.31, 0.74]	Cabozantinib
Pazopanib	NCT00720941 (COMPARZ)	Low	1.05 [0.90, 1.22]	-
Nintedanib	NCT01024920	High (D4, 5)	1.12 [0.70, 1.80]	-
Temsirolimus	NCT00979966	High (D1 t/m 5)	1.76 [0.70, 4.44]	sunitinib
Atezolizumab + Bevacizumab	NCT01984242b (IMmotion150)	High (D4, 5)	1.00 [0.69, 1.45]	-
	NCT02420821	High (D4)	0.83 [0.71, 0.98]	-
Atezolizumab	NCT01984242a	High (D4, 5)	1.19 [0.82, 1.72]	-
Everolimus	NCT01108445 (ASPEN)	High (D4, 5)	1.41 [0.87, 2.28]	sunitinib
	NCT00903175 (RECORD-3)	High (D4, 5)	1.40 [1.14, 1.71]	sunitinib
Lenvantinib + Everolimus	NCT02811861b (CLEAR)	High (D3, 4)	0.65 [0.53, 0.80]	Lenvantinib + Everolimus
Sorafenib	NCT00732914 (SWITCH)	High (D4, 5)	1.19 [0.93, 1.53]	-

* D1 Bias arising from the randomization process
D2 Bias due to deviations from intended intervention
D3 Bias due to missing outcome data
D4 Bias in measurement of the outcome
D5 Bias in selection of the reported result

Table 2. Progression-free survival. Results of pairwise comparisons with sunitinib (intermediate and poor risk groups according to the International Metastatic RCC Database Consortium)

Intervention	RCT number (name)	IMDC risk group	Risk of Bias*	Progression-free survival HR [95% CI]	Clinically relevant in favour of
Avelumab + Axitinib	NCT02684006 (Javelin renal 101)	intermediate	High (D3, 5)	0.71 [0.58, 0.87]	Avelumab + Axitinib
		poor		0.45 [0.30, 0.67]	Avelumab + Axitinib
Lenvantinib + Pembrolizumab	NCT02811861a (CLEAR)	intermediate	High (D3, 4)	0.39 [0.29, 0.52]	Lenvantinib + Pembrolizumab
Nivolumab + Ipilimumab	NCT02231749 (Checkmate 214)	intermediate-poor	High (D4)	0.74 [0.62, 0.88]	Nivolumab + Ipilimumab
Cabozantinib	NCT01835158 (CABOSUN)	intermediate	Some concerns (D5)	0.52 [0.32, 0.83]	Cabozantinib
		poor		0.31 [0.11, 0.90]	Cabozantinib
Lenvantinib + Everolimus	NCT02811861b (CLEAR)	intermediate	High (D3, 4)	0.67 [0.51, 0.88]	Lenvantinib + Everolimus
		poor		0.73 [0.42, 1.28]	Lenvantinib + Everolimus

* D1 Bias arising from the randomization process
D2 Bias due to deviations from intended intervention
D3 Bias due to missing outcome data
D4 Bias in measurement of the outcome
D5 Bias in selection of the reported result

Table 3. Overall survival. Results of pairwise comparisons with sunitinib (all risk groups combined)

Intervention	RCT number (name)	Risk of Bias*	Overall survival HR [95% CI]	Clinically relevant in favour of
Lenvantinib + Pembrolizumab	NCT02811861a (CLEAR)	High (D3)	0.66 [0.49, 0.88]	Lenvantinib + Pembrolizumab
Nivolumab + Ipilimumab	NCT02231749 (Checkmate 214)	Low	0.69 [0.59, 0.81]	Nivolumab + Ipilimumab
Pembrolizumab + Axitinib	NCT02853331 (KEYNOTE-426)	Low	0.73 [0.60, 0.88]	Pembrolizumab + Axitinib
Nivolumab + Cabozantinib	NCT03141177 (CHECKMATE 9ER)	High (D3, 5)	0.60 [0.44, 0.82]	Nivolumab + Cabozantinib
Cabozantinib	NCT02761057	Some concerns (D5)	0.84 [0.47, 1.51]	-
Pazopanib	NCT00720941 (COMPARZ)	Low	0.92 [0.79, 1.07]	-
Nintedanib	NCT01024920	Some concerns (D5)	0.92 [0.54, 1.56]	-
Temsirolimus	NCT00979966	High (D1, 2, 3, 5)	0.98 [0.31, 3.09]	-
Atezolizumab + Bevacizumab	NCT01984242b (IMmotion150)	Some concerns (D5)	1.30 [0.80, 2.12]	sunitinib
	NCT02420821	Low	0.91 [0.76, 1.08]	-
Atezolizumab	NCT01984242a	Some concerns (D5)	1.06 [0.65, 1.73]	-
Everolimus	NCT01108445 (ASPEN)	Some concerns (D5)	1.12 [0.48, 2.60]	-
Lenvantinib + Everolimus	NCT02811861b (CLEAR)	High (D3)	1.15 [0.88, 1.50]	-

* D1 Bias arising from the randomization process
D2 Bias due to deviations from intended intervention
D3 Bias due to missing outcome data
D4 Bias in measurement of the outcome
D5 Bias in selection of the reported result

Table 4. Overall survival. Results of pairwise comparisons with sunitinib (intermediate and poor risk groups according to the International Metastatic RCC Database Consortium)

Intervention	RCT number (name)	IMDC risk group	Risk of Bias *	Overall survival HR [95% CI]	Clinically relevant in favour of
Avelumab + Axitinib	NCT02684006 (Javelin renal 101)	intermediate	High (D3, 5)	0.84 [0.65, 1.08]	-
		poor		0.60 [0.40, 0.91]	Avelumab + Axitinib
Lenvantinib + Pembrolizumab	NCT02811861a (CLEAR)	intermediate	High (D3)	0.72 [0.50, 1.04]	Lenvantinib + Pembrolizumab
		poor		0.30 [0.14, 0.64]	Lenvantinib + Pembrolizumab
Nivolumab + Ipilimumab	NCT02231749 (Checkmate 214)	intermediate-poor	Low	0.65 [0.54, 0.78]	Nivolumab + Ipilimumab
Cabozantinib	NCT01835158 (CABOSUN)	Intermediate-poor	High (D3, 5)	0.80 [0.53, 1.21]	-
Lenvantinib + Everolimus	NCT02811861b (CLEAR)	intermediate	High (D3)	1.22 [0.86, 1.73]	-
		poor		0.90 [0.52, 1.55]	-

* D1 Bias arising from the randomization process
D2 Bias due to deviations from intended intervention
D3 Bias due to missing outcome data
D4 Bias in measurement of the outcome
D5 Bias in selection of the reported result

Table 5. SAEs. Results of pairwise comparisons with sunitinib (all risk groups combined)

Intervention	RCT number (name)	Risk of Bias*	SAEs RR [95% CI]	Clinically relevant In favour of
Lenvantinib + Pembrolizumab	NCT02811861a (CLEAR)	High (D2, 4)	1.52 [1.27, 1.83]	sunitinib
Nivolumab + Ipilimumab	NCT02231749 (Checkmate 214)	High (D2)	1.40 [1.23, 1.59]	sunitinib
Pembrolizumab + Axitinib	NCT02853331 (KEYNOTE-426)	Low	1.29 [1.07, 1.55]	sunitinib
Cabozantinib	NCT01835158 (CABOSUN)	High (D2, 5)	0.92 [0.68, 1.26]	-
Pazopanib	NCT00720941 (COMPARZ)	Some concerns (D2)	0.99 [0.87, 1.14]	-
Nintedanib	NCT01024920	High (D2, 4, 5)	0.91 [0.50, 1.66]	-
Temsirolimus	NCT00979966	High (D1, 2, 4, 5)	0.97 [0.48, 1.95]	-
Atezolizumab + Bevacizumab	NCT01984242 (IMmotion151)	Some concerns (D4, 5)	1.73 [1.19, 2.52]	sunitinib
	NCT02420821	High (D2)	1.11 [0.95, 1.31]	-
Atezolizumab	NCT01984242a	Some concerns (D4, 5)	1.28 [0.85, 1.93]	sunitinib
Everolimus	NCT01108445 (ASPEN)	High (D2, 4, 5)	0.79 [0.62, 1.00]	everolimus
	NCT00903175 (RECORD-3)	Some concerns (D5)	1.03 [0.88, 1.20]	-
Lenvantinib + Everolimus	NCT02811861b (CLEAR)	High (D2)	1.39 [1.15, 1.68]	sunitinib
Sorafenib	NCT00732914 (SWITCH)	High (D4, 5)	1.08 [0.87, 1.34]	-

* D1 Bias arising from the randomization process
D2 Bias due to deviations from intended intervention
D3 Bias due to missing outcome data
D4 Bias in measurement of the outcome
D5 Bias in selection of the reported result

Adverse events
The outcome serious adverse events was reported for all risk groups combined in 14 trials. In the only trial at low risk of bias for this outcome, the effect of pembrolizumab + axitinib was clinically relevant in favour of sunitinib (HR [95% CI] 1.29 [1.07, 1.55]. In only one trial a clinically relevant effect estimate was reported in favour of the intervention, everolimus (HR [95% CI] 0.79 [0.62, 1.00]), but this trial had a high risk of bias. Clinically relevant effects in favour of sunitinib were reported for lenvantinib + pembrolizumab (HR [95% CI] 1.52 [1.27, 1.83]), nivolumab +ipilimumab (HR [95% CI] 1.40 [1.23, 1.59]), lenvantinib + everolimus (HR [95% CI] 1.39 [1.15, 1.68]), in trials at high risk of bias, and for atezolizumab + bevacizumab (HR [95% CI] 1.73 [1.19, 2.52]) and atezolizumab (HR [95% CI] 1.28 [0.85, 1.93]) in trials with some concerns for risk of bias.

The outcome serious adverse events was not reported for the IMDC intermediate and poor risk groups separately.

Level of evidence of the literature
Evidence from RCTs starts at the level high GRADE.

Progression-free survival – all risk groups combined
The level of evidence for *pazopanib compared to sunitinib* regarding the outcome measure progression free survival was not downgraded. High GRADE.

The level of evidence for *lenvantinib + pembrolizumab, pembrolizumab + axitinib, nivolumab + cabozantinib, lenvantinib + everolimus compared to sunitinib* regarding the outcome measure progression free survival was downgraded by one level to a moderate GRADE because of study limitations (risk of bias).

The level of evidence for *nivolumab + ipilimumab, cabozantinib, atezolizumab, everolimus, sorafenib compared to sunitinib* regarding the outcome measure progression free survival was downgraded by two levels to a low GRADE, one level because of study limitations (risk of bias) and one level because the lower margin of clinical relevance was crossed by the 95% confidence interval (imprecision).

The level of evidence for *nintedanib, temsirolimus, atezolizumab + bevacizumab compared to sunitinib* regarding the outcome measure progression free survival was downgraded by three levels to a very low GRADE, one level because of study limitations (risk of bias) and two levels because both the lower and upper margins of clinical relevance were crossed by the 95% confidence interval (imprecision).

Overall survival – all risk groups combined
The level of evidence for *nivolumab + ipilimumab, pembrolizumab + axitinib, nivolumab + cabozantinib, pazopanib, atezolizumab + bevacizumab compared to sunitinib* regarding the outcome measure overall survival was downgraded by one level to a moderate GRADE because of study limitations (risk of bias).

The level of evidence for *lenvantinib + pembrolizumab, lenvantinib + everolimus compared to sunitinib* regarding the outcome measure overall survival was downgraded by two levels to a low GRADE, one level because of study limitations (risk of bias) and one level because one of the margins of clinical relevance was crossed by the 95% confidence interval (imprecision).

The level of evidence for *cabozantinib, nintedanib, temsirolimus, atezolizumab, everolimus compared to sunitinib* regarding the outcome measure overall survival was downgraded by three levels to a very low GRADE, one level because of study limitations (risk of bias) and two levels because both the lower and upper margins of clinical relevance were crossed by the 95% confidence interval (imprecision).

Quality of life – all risk groups combined
The level of evidence for *pazopanib compared to sunitinib* regarding the outcome measure quality of life was downgraded by three levels to a very low GRADE, one level because of study limitations (risk of bias) and two levels because the number of participants with this outcome was extremely small (n=4)(imprecision).

Adverse events – all risk groups combined
The level of evidence for *pembrolizumab + axitinib compared to sunitinib* regarding the outcome measure adverse events was downgraded by one level to a moderate GRADE because the upper margin of clinical relevance was crossed by the 95% confidence interval (imprecision).

The level of evidence for *lenvantinib + pembrolizumab, pazopanib, everolimus compared to sunitinib* regarding the outcome measure adverse events was downgraded by one level to a moderate GRADE because of study limitations (risk of bias).

The level of evidence for *nivolumab + ipilimumab, atezolizumab + bevacizumab, atezolizumab, lenvantinib + everolimus, sorafenib compared to sunitinib* regarding the outcome measure adverse events was downgraded by two levels to a low GRADE, one level because of study limitations (risk of bias) and one level because one of the margins of clinical relevance was crossed by the 95% confidence interval (imprecision).

The level of evidence for *cabozantinib, nintedanib, temsirolimus compared to sunitinib* regarding the outcome measure adverse events was downgraded by three levels to a very low GRADE, one level because of study limitations (risk of bias) and two levels because both the lower and upper margins of clinical relevance were crossed by the 95% confidence interval (imprecision).

Conclusions

Progression-free survival – all risk groups combined

High GRADE	Pazopanib makes little or no difference in progression-free survival compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Moderate GRADE	Lenvantinib + pembrolizumab, pembrolizumab + axitinib, *nivolumab + cabozantinib,* lenvantinib + everolimus probably improve progression-free survival compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Low GRADE	Nivolumab + ipilimumab, atezolizumab, sorafenib may make little or no difference in progression-free survival compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Low GRADE	Cabozantinib may improve progression-free survival compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Overall survival

Moderate GRADE	Nivolumab + ipilimumab, pembrolizumab + axitinib, *nivolumab + cabozantinib* probably improve overall survival compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Moderate GRADE	Pazopanib, atezolizumab + bevacizumab probably make little or no difference in overall survival compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Low GRADE	Lenvantinib + pembrolizumab may improve overall survival compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Low GRADE	Lenvantinib + everolimus may make little or no difference in overall survival compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

- GRADE	The evidence is very uncertain about the effect of cabozantinib, nintedanib, temsirolimus, atezolizumab, everolimus on overall survival compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma since no data were reported. *Source: Aldin, 2023.*

Quality of Life

Very low GRADE	The evidence is very uncertain about the effect of pazopanib on Quality of Life compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

- GRADE	No conclusion could be drawn about the effect of lenvantinib +pembrolizumab, nivolumab + ipilimumab, pembrolizumab + axitinib, cabozantinib, nintedanib, temsirolimus, atezolizumab + bevacizumab, atezolizumab, everolimus, lenvantinib + everolimus, sorafenib on quality of life since no data were reported. *Source: Aldin, 2023.*

Adverse events

Moderate GRADE	Pembrolizumab + axitinib, lenvantinib + pembrolizumab, everolimus probably result in more serious adverse events compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Moderate GRADE	Pazopanib probably results in little or no difference in serious adverse events compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Low GRADE	Nivolumab + ipilimumab, atezolizumab + bevacizumab, atezolizumab, lenvantinib + everolimus, sorafenib may result in more serious adverse events compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Very low GRADE	The evidence is very uncertain about the effect of cabozantinib, nintedanib, temsirolimus on adverse events compared to sunitinib in formerly untreated patients with metastatic renal cell carcinoma. *Source: Aldin, 2023.*

Summary of conclusions

	PFS	OS	QoL	SAEs
Lenvantinib + Pembrolizumab	Probably improves	May improve	No data	Probably deteriorates
Nivolumab + Ipilimumab	May make little or no difference	Probably improves	No data	May deteriorate
Pembrolizumab + Axitinib	Probably improves	Probably improves	No data	Probably deteriorates
Cabozantinib	May improve	Very uncertain	No data	Very uncertain
Cabozantinib + Nivolumab	Probably improves	Probably improves	No data	
Pazopanib	Makes little or no difference	Probably makes little or no difference	Very uncertain	Probably makes little or no difference
Nintedanib	Very uncertain	Very uncertain	No data	Very uncertain
Temsirolimus	Very uncertain	Very uncertain	No data	Very uncertain
Atezolizumab + Bevacizumab	Very uncertain	Probably makes little or no difference	No data	May deteriorate
Atezolizumab	May make little or no difference	Very uncertain	No data	May deteriorate
Everolimus	May deteriorate	Very uncertain	No data	Probably deteriorates
Lenvantinib + Everolimus	Probably improves	May make little or no difference	No data	May deteriorate
Sorafenib	May make little or no difference	No data	No data	May deteriorate

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

In de uitgebreide systematic review en network meta-analysis van Aldin (2023) worden een aantal systemische behandelingen vergeleken. Voor de cruciale uitkomsten progressie-vrije overleving en overall survival lijken de combinaties lenvatinib + pembrolizumab, nivolumab + ipilimumab,pembrolizumab + axitinib en nivolumab + cabozantinib de meest gunstige behandelingen. Deze combinaties komen er geen van allen gunstig uit wanneer gekeken wordt naar de belangrijke uitkomst serious adverse events, en voor de uitkomst Kwaliteit van Leven zijn er onvoldoende data gerapporteerd. De bewijskracht voor de cruciale uitkomsten voor deze vier combinaties varieert van laag tot redelijk. De meeste behandelingen zijn vergeleken met sunitinib, en niet met elkaar; daardoor is er geen directe onderlinge vergelijking mogelijk. Bij bijna alle geïncludeerde trials was niet duidelijk of degenen die patiënten includeerden geblindeerd waren voor de volgorde van de randomisatie; dat kan ertoe geleid hebben dat de groepen bij baseline een verschillende prognose hadden. Daarnaast was er bij veel uitkomsten sprake van imprecisie, waarbij de betrouwbaarheidsintervallen zo breed waren dat er geen uitsluitsel werd gegeven over klinische relevantie.

Afhankelijk van de risico-groep waarin de patiënt valt, zullen de verschillende opties voor systemische therapie besproken worden, met inachtneming van de kansen op verlenging van progressievrije overleving en overall survival, alsmede de kans op mogelijke bijwerkingen.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Keuzen omtrent het al dan niet starten van systemische therapie en de soort systemische therapie zullen te allen tijde door middel van shared decision making tussen patiënt, de naasten en de behandelaren gemaakt worden. Deze keuzen zullen worden ingegeven door de risicogroep waarin patiënt zich bevindt en de mogelijke voor- en nadelen betreffende levensduur en kwaliteit van leven die de behandeling met zich mee kan brengen en door wat voor patiënten belangrijk is in het leven.

Kosten (middelenbeslag)

De steeds stijgende kosten van systemische therapie voor patiënten in alle risicogroepen met gevorderd niercelcarcinoom zijn een belangrijk punt van maatschappelijke zorg voor het beschikbaar houden van alle therapeutische opties voor deze patiënten in de toekomst.

Aanvaardbaarheid, haalbaarheid en implementatie

Mits uitgevoerd in centra met de volgens de geldende afspraken in de geeigende landelijke gremia vereiste expertise en organisatie van zorg, zijn de momenteel beschikbare systemische therapieën voor patiënten met gevorderd niercelcarcinoom uitvoerbaar en van voldoende meerwaarde om deze toe te passen.

Aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Voor patiënten met gevorderd niercelcarcinoom, dienen onderstaande systemische therapieën besproken te worden, gezien de aangetoonde meerwaarde van deze behandelingen. Dit dient te geschieden met inachtneming van de risico-groep waarin patiënt zich bevindt en door middel van shared decision making, gezien de multipele opties die voorhanden zijn.

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.

Bied bij patiënten met gemetastaseerd heldercellig niercelcarcinoom met intermediair of ongunstige IMDC Risico score kenmerken behandeling met ipilimumab + nivolumab of pembrolizumab + axitinib of nivolumab + cabozantinib of Lenvatinib + pembrolizumab aan.

Overweeg cabozantinib, sunitinib of pazopanib voor patiënten met intermediair of ongunstige IMDC Risico score kenmerken die een contra-indicatie voor immuuntherapie hebben.

Overweeg met de patiënt uitstel van de start van systemische therapie voor gemetastaseerd niercelcarcinoom bij een zorgvuldig geselecteerde groep met een relatief indolent ziektebeloop. Zie hiervoor ook de module over Uitgestelde Behandeling.

Registreer de IMDC Risico score (gunstig, intermediair, ongunstig) bij iedere patiënt met gemetastaseerd niercelcarcinoom in de conclusie van het multidisciplinair overleg.

Kennislacunes

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

Literatuur

Aldin A, Besiroglu B, Adams A, Monsef I, Piechotta V, Tomlinson E, Hornbach C, Dressen N, Goldkuhle M, Maisch P, Dahm P. First-line therapy for adults with advanced renal cell carcinoma: a systematic review and network meta-analysis. Cochrane Database of Systematic Reviews. 2023(5).

Module 3 Optimale eerstelijns systeemtherapie niet-heldercellig niercelcarcinoom

Uitgangsvraag
Welke eerstelijns systeemtherapie heeft de voorkeur bij patiënten met gemetastaseerd niet-heldercellig niercelcarcinoom?

Inleiding
In de behandeling van patienten met een gemetastaseerd heldercellig niercelcarcinoom zijn het afgelopen decennium veel middelen ter beschikking gekomen (zie module Keuze eerstelijns systemische therapie heldercellig niercelcarcinoom). In het verleden werden therapie opties bij het niet-heldercellig niercelcarcinoom toegepast naar aanleiding van extrapolatie van gegevens bij het heldercellig niercelcarcinoom of zeer beperkte observaties. Complex blijft dat niet-heldercellig niercelcarcinoom nog steeds een heterogene groep is, waarbij de patientenaantallen relatief laag zijn. Er is momenteel geen uniform behandeladvies in de landelijke richtlijn.

Search and select
A systematic review of the literature was performed to answer the following 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?

P: patients	patients with metastatic non-clear cell renal cell carcinoma (nccRCC)
I: intervention	immunotherapy and/or targeted therapy
C: control	sunitinib
O: outcome measure	1) Progression-free survival rate, 2) overall survival rate, 3) quality of life and 4) complications

Relevant outcome measures
The guideline development group considered progression-free survival rate and overall survival rate as a critical outcome measures for decision making; and quality of life and complications as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a relative risk (RR) or hazard ratio (HR) < 0.80 or >1.25 as a minimal clinically (patient) important difference for dichotomous or survival variables, and >0.5 SD for continuous variables.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2011 until December 31st 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 431 hits. Studies that met the following criteria were eligible for selection: studies reporting original data, systematic reviews, randomized controlled trials (RCTs) and observational comparative studies reporting on various combinations of immunotherapy and targeted therapy with each other or with sunitinib in patients with metastatic non-clear cell renal carcinoma. Twenty-eight studies were initially selected based on title and abstract screening. After reading the full text, 26 studies were excluded (see the table with reasons for exclusion under

the tab Methods), and 2 studies were included. Two other RCTs (Bergmann, 2020; Choueiri, 2020) were also included by reviewing reference list of included studies.

Results

One systematic review (Osterman, 2020) and one randomized, open-label, phase II trial (Pal, 2021) were included in the analysis of the literature. Systematic review of Osterman included 31 studies, of which 3 RCTs (Armstrong, 2016; Tannir, 2016 and Motzer, 2014) matched our PICO criteria. Two other RCTs (Bergmann, 2020; Choueiri, 2020) were also included by reviewing reference list of included studies. Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature

Description of studies

Systematic Review by Osterman (2020) evaluated systemic treatment options in locally advanced or metastatic nccRCC between 2000-2019. Randomized controlled trials, single-arm phase II–IV trials, and prospective analyses of medication access programs were included. The primary outcome measures were progression free survival (PFS), overall survival (OS), and objective response rate (ORR).

Armstrong (2016) enrolled patients with metastatic papillary, chromophobe, or unclassified non-clear-cell renal cell carcinoma with no history of previous systemic treatment to compare the mTOR inhibitor everolimus and the VEGF receptor inhibitor sunitinib in patients with non-clear-cell renal cell carcinoma (ASPEN). Patients were randomly assigned (1:1) to receive everolimus (10 mg/day) or sunitinib (50 mg/day; 6-week cycles of 4 weeks with treatment followed by 2 weeks without treatment) administered orally until disease progression or unacceptable toxicity. Randomisation was stratified by Memorial Sloan Kettering Cancer Center risk group and papillary histology.

Tannir (2016) conducted a randomized phase 2 trial (ESPN) comparing sunitinib and everolimus in non–clear cell RCC (non-ccRCC). Patients with metastatic, non-ccRCC, or ccRCC with >20% sarcomatoid features (ccSRCC) were randomized to receive sunitinib or everolimus with crossover at disease progression. Primary end point was progression-free survival (PFS) in first-line therapy; 108 patients were needed to show improvement in median PFS (mPFS) from 12 wk with sunitinib to 20 wk with everolimus. Patients were stratified by Memorial Sloan Kettering Cancer Center risk group [19] and histologic RCC subtype (papillary vs other), and they were randomized 1:1 to receive either everolimus or sunitinib.

Motzer (2014) conducted a multicenter, randomized phase II trial (RECORD-3) to compare first-line everolimus followed by sunitinib at progression with the standard sequence of first-line sunitinib followed by everolimus in patients with metastatic renal cell carcinoma. RECORD-3 used a crossover treatment design. The primary objective was to assess progression-free survival (PFS) noninferiority of first-line everolimus compared with first-line sunitinib. Secondary end points included combined PFS for each sequence, overall survival (OS), and safety. The population comprised patients age 18 years or older who had measurable version clear cell or non–clear cell mRCC, with or without nephrectomy. Key eligibility criteria included no prior systemic therapy; a Karnofsky performance status of 70% or greater; adequate hematologic, liver, and kidney function; and normal left ventricular ejection fraction.

Bergmann (2020) performed a prospectively randomized phase IIa multicenter trial, investigating temsirolimus (TEM) versus sunitinib (SUN) as first-line therapy in patients with metastatic nccRCC. The patients were randomized 1: 1 to either TEM in a dose of 25 mg i.v. once a week or SUN with 50 mg p.o. daily for 4 weeks on and 2 weeks off. Primary endpoint was progression-free survival (PFS). In total, 22 patients were included with predominantly papillary RCC (16/22) followed by chromophobe RCC and others. This trial had to be terminated due to low recruitment.

Choueiri (2020) conducted a phase 3, open-label, randomized clinical trial (SAVOIR) to investigate efficacy of savolitinib vs sunitinib in patients with MET-Driven papillary renal cell carcinoma. Overall, 360 to 450 patients were to be screened to randomize approximately 180 patients. Patients were adults with MET-driven (centrally confirmed), metastatic PRCC, with 1 or more measurable lesions. Overall, 254 patients were screened. Patients received 600mg of savolitinib orally once daily (qd), or 50mg of sunitinib orally qd for 4 weeks, followed by 2 weeks without treatment. The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), objective response rate (ORR), duration of response, and safety/tolerability. Premature termination of the study and the limited number of patients randomized were key limitations of this study.

Pal (2021) conducted a randomized, open-label, phase II trial involving 147 patients with metastatic papillary renal cell carcinoma (PRCC) who had received up to one prior therapy (excluding vascular endothelial growth factor-directed agents). They aimed to compare the effectiveness and safety of an existing standard (sunitinib) to MET kinase inhibitors (cabozantinib, crizotinib, and savolitinib). The patients were randomly assigned to receive sunitinib (46 patients), cabozantinib (n=44), savolitinib (n=29) and crizotinib (n=28), with stratification by receipt of prior therapy and PRCC subtype, until their disease progressed or they had unacceptable side effects. Progression-free survival (PFS) was the primary endpoint. The trial was then temporarily stopped for savolitinib and crizotinib arms because of hazard ratio for PFS greater than 1 relative to sunitinib.

Results

nccRCC subtypes

Papillary
1) Progression-free survival (PFS) rate

In the Pal trial, the MET inhibitor cabozantinib demonstrated a median PFS of 9.0 months (95% CI: 5.6–12.4) compared to 5.6 months (95% CI: 2.9–6.7) for sunitinib. The hazard ratio (HR) for PFS favored cabozantinib over sunitinib significantly (HR: 0.60, 95% CI: 0.37–0.97). This is considered a clinically relevant difference. In addition to comparing cabozantinib and sunitinib, an additional 57 patients were inrolled to crizotinib and savolitinib arms. Both arms were closed due to hazard ratio for PFS greater than 1 at prespecified interim analysis. Savolitinib and crizotinib did not improve PFS relative to sunitinib.

Additionally, in the SAVOIR trial, the MET inhibitor savolitinib showed a median PFS of 7.0 months (95% CI: 2.8–not calculated) compared to 5.6 months (95% CI: 4.1–6.9) for sunitinib. This was not a statistically significance but a clinically relevant difference between the arms (HR 0.71, 95% CI 0.37–1.36, p = 0.31).

In the ESPN trial, the mTOR inhibitor everolimus exhibited a median PFS of 4.1 months (95% CI: 1.5–7.4) compared to 5.7 months (95% CI: 1.4–19.8) for sunitinib.

In the ASPEN trial, the MET inhibitor sunitinib showed a median PFS of 8.1 months (95% CI: 5.8–11.1), while the mTOR inhibitor everolimus exhibited a median PFS of 5.5 months (95% CI: 4.4–5.6).

2) Overall survival (OS) rate

In the Pal trial, the overall survival did not significantly differ among the treatment groups. The hazard ratio for the survival comparison between cabozantinib and sunitinib was 0.84 (95%CI, 0.47–1.51). The reported median overall survival was 16.4 months (95% CI, 12.8–21.6) for the sunitinib arm, 20.0 months (95% CI, 11.3-Not calculated) for the cabozantinib arm, 19.9 months (95% CI, 11.2-NR) for the crizotinib arm, and 11.7 months (95% CI, 6.7-28.9)for the savolitinib arm.

Similarly, in the SAVOIR trial, no significant difference was observed in overall survival between treatment arms. The hazard ratio for overall survival comparison between savolitinib and sunitinib was 0.51 (95% CI, 0.21–1.17), indicating no significant difference but a clinically relevant difference. The median overall survival was not reached for the savolitinib group and was 13.2 months (95% CI, 7.6-NC) for the sunitinib group.

In the ASPEN trial, no differences in overall survival were noted within subsets of patients according to treatment group assignment.

In the ESPN trial, the median overall survival was 14.9 months (95% CI,7.1-22.1) for the everolimus arm and 16.6 months (95% CI ,5.9-NA) for the sunitinib arm.

3) Quality of life

In the SAVOIR trial, the effect of treatment on health-related quality of life and disease-related symptoms, as assessed by FACIT-F and FKSI-19 scores, revealed no significant variances between treatment arms. Notably, compliance rates were higher in the savolitinib arm compared to the sunitinib arm for both FACIT-F (91% vs. 78%, respectively) and FKSI-19 (88% vs. 67%, respectively) questionnaires.

EQ-5D-5L scores indicated fewer patients in the savolitinib group reported severe issues with pain/discomfort and anxiety/depression compared to the sunitinib group. Specifically, there was a change of 1 in score from baseline for savolitinib (n = 6) versus -12 for sunitinib (n = 6). Additionally, compliance rates were higher in the savolitinib group compared to the sunitinib group (88% vs. 67%, respectively).

4) Complications

In both the Pal and SAVOIR trials, which investigated MET inhibitors, adverse events were notable among patients receiving these inhibitors compared to those receiving sunitinib.

In the Pal trial, grade 3 or 4 adverse events occurred in 69%, 74%, 37%, and 39% of patients receiving sunitinib, cabozantinib, crizotinib, and savolitinib, respectively. Additionally, one grade 5 thromboembolic event was observed with cabozantinib. Treatment discontinuation

due to adverse events attributed to study medication was highest with sunitinib (24%), followed by cabozantinib (23%), crizotinib (16%), and savolitinib (10%).

Similarly, in the SAVOIR trial, adverse events were reported in a significant proportion of patients receiving MET inhibitors. Specifically, grade 3 or higher adverse events were observed in 42% and 81% of patients receiving savolitinib and sunitinib, respectively. Moreover, adverse events led to dose modifications in 30% and 74% of patients receiving savolitinib and sunitinib, respectively. Notably, adverse events of any cause occurred in 91% of patients in the savolitinib group and 100% of patients in the sunitinib group. Additionally, all deaths attributed to adverse events occurred in the sunitinib group.

Non-clear cell other than papillary
1) Progression-free survival rate

The ASPEN and ESPN trials provided insights into the progression-free survival (PFS) outcomes specifically for the subgroup of chromophobe patients. In contrast to the overall trial results, both trials demonstrated a longer median PFS duration in the everolimus group compared to the sunitinib group. In the ASPEN trial, the median PFS was 11.4 months for everolimus and 5.5 months for sunitinib among chromophobe patients. Similarly, in the ESPN trial, the median PFS was not reached for everolimus and 8.9 months for sunitinib, although these differences were non-significant.

Specifically, in the ASPEN trial, among chromophobe patients, patients in the sunitinib group had a median PFS of 5.5 months (80% CI, 3.3–19.7), while the median PFS for everolimus was 11.4 months (80% CI, 5.7–19.4). Moreover, among patients WITH unclassified histology in the ASPEN trial, 15 out of 22 patients in the sunitinib group had a median PFS of 11.5 months (95% CI, 5.3–not reached), while the median PFS for everolimus was 5.7 months (95% CI, 2.8–7.2).

In the ESPN trial, the overall median PFS for everolimus was 3.0 months (95% CI, 1.3–NA), and for sunitinib, it was 7.5 months (95% CI, 3.1–16.7).

2) Overall survival rate

In the ESPNtrial, the overall median overall survival for everolimus was 15.7 months (95% CI: 4.7–NA) and for sunitinib was 17.6 (95% CI: 9.6–NA).

3) Quality of life
The included literature did not report on this outcome measure.

4) Complications
The included literature did not report on this outcome measure.

Treatments of nccRCC

mTOR inhibitor vs sunitinib
Everolimus versus sunitinib
There were 3 RCTs comparing the mammalian target of rapamycin (mTOR) inhibitor everolimus to the vascular endothelial growth factor (VEGF) TKI sunitinib in first line treatment of metastatic nccRCC. The ASPEN and ESPN trials enrolled only nccRCC, and the

RECORD-3 trial enrolled patients with any RCC histology but reported PFS results for nccRCC alone.

1. Progression-free survival rate

The median PFS was numerically longer with first line sunitinib compared to everolimus in all 3 trials, but was only statistically significant and clinically relavnt in the ASPEN (8.3 months vs. 5.6 months; HR 1.41 (80% CI 1.03–1.92)) and RECORD-3 (7.2 months vs. 5.1 months; HR 1.5 (95% CI 0.9–2.8)) trials.

2. Overall survival rate

Median overall survival was numerically greater in the sunitinib group compared to the everolimus group in both ASPEN (31.5 months vs. 13.2 months; HR 1.12 (95% CI 0.7–2.1)) and ESPN (16.2 months vs. 14.9 months; stratified log-rank p = 0.18), however this failed to reach statistical significance and clinical relevance in either trial. Response rates were reported in ASPEN and ESPN with higher ORR seen for the sunitinib group in both trials (18% vs. 9% and 9% vs. 3%, respectively).

3. Quality of life

In the longitudinal sensitivity analysis of RECORD-3, EORTC QLQ-C30 global health status/quality of life and fatigue scores, which were previously equivocal, demonstrated a significant benefit to everolimus. Also, results demonstrated that everolimus as firstline treatment in mRCC does not impair patient quality of life.
In ASPEN at baseline, the median FACT-KSI score was 47·5 (IQR 23–59) for patients in the everolimus group and 45 (27–56) in the sunitinib group. By the third cycle, the median KSI was 44 (IQR 37–50) for everolimus (change from baseline of −4·5, n=31) and 43 (36–49) for sunitinib (change from baseline −1·0, n=33). At progression or end of treatment, median FACT-KSI score was 44 (32–50) for everolimus (change from baseline −7·5) and 42 (31–48) for sunitinib (change from baseline −5·0). Between-group differences in quality-of-life measures, including disease-related subscales, were not significant nor clinically relevant.

4. Complications

Common treatment-emergent adverse events in RECORD-3 during first-line everolimus or sunitinib were stomatitis (53% and 57%, respectively), fatigue (45% and 51%, respectively), and diarrhea (38% and 57%, respectively).
In ASPEN overall, 40 (78%) patients receiving sunitinib had grade 3 or worse treatment-related adverse event compared with 34 (60%) patients receiving everolimus. Serious adverse events (grade 3–5) that were felt to be at least possibly related to study treatment per protocol were reported in 34 (60%) of everolimus-treated patients and 40 (78%) of sunitinib-treated patients.
In ESPN, any grade 3 or 4 AE occurred in 29 of 33 patients (88%) who received first-line sunitinib and in 19 of 35 patients (54%) who received first-line everolimus. Common grade 3 or 4 sunitinib-associated treatment-emergent AEs included fatigue (36%), hypertension (18%), diarrhea (21%), neutropenia (27%), and hyponatremia (15%). Grade 3 anemia occurred in 11% of patients who received everolimus.

<u>Temsirolimus vs sunitinib</u>

1. Progression-free survival rate

In the study by Bergmaan, temsirolimus was compared to sunitinib in 22 patients with advanced RCC. This trial did not achieve its prespecified endpoint, as the difference in median PFS between sunitinib and temsirolimus, 13.2 vs 9.3 months (HR 1.64; 95% CI 0.65–4.18 in favor of sunitinib), was not statistically significant but clinically relevant.

2. Overall survival rate

There was also no significant difference in median OS, 19.8 vs. 19.4 months.

3. Quality of life

The included literature did not report on this outcome measure.

4. Complications

Eleven of 12 patients had drug-related severe adverse events (SAE) in the Temsirolimus arm and all patients in the sunitinib arm.

MET inhibitor vs sunitinib

Savolitinib vs sunitinib

1. Progression-free survival rate

Choueiri (2020) In terms of PFS, there was not a statistically significance but a clinically relevant difference between the arms (HR 0.71, 95% CI 0.4–1.4, p = 0.31). Median PFS was 7.0 months (95% CI 2.8- not calculated) in the savolitinib arm and 5.6 months (95% CI 4.1–6.9) in the sunitinib arm.

2. Overall survival rate

There was also not a significant difference in terms of OS (HR 0.51, 95% CI 11.9-not calculated, p = 0.11). This is considered a clinically relevant difference.

3. Quality of life

The impact of treatment on health-related quality of life and disease-related symptoms based on the FACIT-F scores and FKSI-19 scores showed no notable differences between treatment groups. Compliance was higher in the savolitinib group compared with the sunitinib group for both the FACIT-F questionnaire (91% vs 78%, respectively) and the FKSI-19 questionnaire (88% vs 67%, respectively).

The EQ-5D-5L scores showed fewer patients reporting severe problems in pain/discomfort and anxiety/depression in the savolitinib group than in the sunitinib group: there was a change from baseline of 1 in score for savolitinib (n = 6) compared with -12 for sunitinib (n = 6). Furthermore, compliance was higher in the savolitinib group compared with sunitinib group (88% vs 67%, respectively).

4. Complications

For savolitinib and sunitinib respectively, grade 3 or higher adverse events (AEs) were reported in 14 (42%) and 22 (81%) of patients and AE-related dose modifications in 10 (30%) and 20 (74%). Adverse events (AEs) of any cause occurred in 30 of 33 (91%) of the savolitinib group and 100% of the sunitinib group. Twenty-two patients died during the study;with 3 deaths attributed to AEs, all in the sunitinib group.

Cabozantinib, crizotinib and savolitinib vs sunitinib

1. Progression-free survival rate

Median PFS was 9.0 months (95% CI 5.6–12.4) for cabozantinib and 5.6 months (95% CI 2.9–6.7) for sunitinib, with significantly improved HR for PFS of 0.60 (95% CI 0.37–0.97). This is considered a clinically relevant difference.

In addition to comparing cabozantinib and sunitinib, an additional 57 patients were inrolled to crizotinib and savolitinib arms. Both arms were closed due to hazard ratio for

PFS greater than 1 at prespecified interim analysis. Savolitinib and crizotinib did not improve PFS relative to sunitinib.

2. Overall survival rate

There was no significant difference in overall survival between the four treatment groups, with reported median OS of 20.0 months (95% CI 11.3-Not calculated) in the cabozantinib arm and 16.4 months (95% CI 12.8–21.6) in the sunitinib arm.

3. Quality of life

The included literature did not report on this outcome measure.

4. Complications

Grade 3 or 4 adverse events occurred in 69%, 74%, 37% and 39% of patients receiving sunitinib, cabozantinib, crizotinib and savolitinib, respectively; one grade 5 thromboembolic event was seen with cabozantinib.

Level of evidence of the literature

Systematic reviews of RCTs for therapeutic research questions start at high GRADE.

mTOR inhibitor vs sunitinib

Everolimus versus sunitinib

The level of evidence regarding the outcome measure **progression-free survival rate** was downgraded by one level because of the relatively small number of included patients (imprecision) to Moderate GRADE.

The level of evidence regarding the outcome measure **overall survival rate** was downgraded by one level because of the relatively small number of included patients (imprecision) to moderate GRADE.

The level of evidence regarding the outcome measure **quality of life** was downgraded by one level because of the relatively small number of included patients (imprecision) to moderate GRADE.

The level of evidence regarding the outcome measure **complications** was downgraded by one level because of the relatively small number of included patients (imprecision) to moderate GRADE.

Temsirolimus vs sunitinib

The level of evidence regarding the outcome measure **progression-free survival rate** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to low GRADE.

The level of evidence regarding the outcome measure **overall survival rate** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to low GRADE.

The level of evidence regarding the outcome measure **complications** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to low GRADE.

Due to lack of evidence, no grading was possible for the outcome measures **quality of life**.

MET inhibitor vs sunitinib

Savolitinib vs sunitinib

The level of evidence regarding the outcome measure **progression-free survival rate** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to low GRADE.

The level of evidence regarding the outcome measure **overall survival rate** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to low GRADE.

The level of evidence regarding the outcome measure **quality of life** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to low GRADE.

The level of evidence regarding the outcome measure **complications** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to low GRADE.

Cabozantinib, crizotinib and savolitinib vs sunitinib

The level of evidence regarding the outcome measure measures **progression-free survival rate** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to very low GRADE.

The level of evidence regarding the outcome measure **overall survival rate** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to low GRADE.

The level of evidence regarding the outcome measure **complications** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to low GRADE.

Due to lack of evidence, no grading was possible for the outcome **quality of life**.

Conclusions

mTOR inhibitor vs sunitinib

Everolimus versus sunitinib

Moderate GRADE	Sunitinib probably results in an increase in **progression-free survival rate** when compared with everolimus in patient population with non clear cell RCC. *Source: Osterman, 2020*

Moderate GRADE	Sunitinib probably results in little to no difference in **overall survival** when compared with everolimus in patients with non clear cell RCC. *Source: Osterman, 2020*

Moderate GRADE	Everolimus probably results in little to no difference in **quality of life** when compared with sunitinib in patient population with non clear cell RCC. *Source: Osterman, 2020*

Moderate GRADE	Everolimus probably reduces **complications** slightly when compared with sunitinib in patient population with non clear cell RCC. *Source: Osterman, 2020*

Temsirolimus vs sunitinib

Low GRADE	The evidence suggests that temsirolimus results in little to no difference in **progression-free survival rate** when compared with sunitinib in patient population with non clear cell RCC. Source: Bergmann, 2020

Low GRADE	The evidence suggests that temsirolimus results in little to no difference in **overall survival** when compared with sunitinib in patient population with non clear cell RCC. Source: Bergmann, 2020

No GRADE	No evidence was found regarding the effect of temsirolimus on **quality of life** when compared with sunitinib in patient with non clear cell RCC.

Low GRADE	The evidence suggests that temsirolimus results in little to no difference in **complications** when compared with sunitinib in patient population with non clear cell RCC. Source: Bergmann, 2020

MET inhibitor vs sunitinib

Savolitinib vs sunitinib

Low GRADE	The evidence suggests that savolitinib results in little to no difference in **progression-free survival rate** when compared with sunitinib in patient population with non clear cell RCC. *Source: Choueiri, 2020*

Low GRADE	The evidence suggests that savolitinib results in little to no difference in **overall survival** when compared with sunitinib in patient population with non clear cell RCC. *Source: Choueiri, 2020*

Low GRADE	The evidence suggests that savolitinib results in little to no difference in **quality of life** when compared with sunitinib in patient population with non clear cell RCC. *Source: Choueiri, 2020*

Low GRADE	Savolitinib may reduce **complications** when compared with sunitinib in patient population with non clear cell RCC. *Source: Choueiri, 2020*

Cabozantinib, crizotinib and savolitinib vs sunitinib

Low GRADE	The evidence suggests Cabozantinib increases **progression-free survival rate** when compared with sunitinib in patient population with metastatic papillary renal cell carcinoma. *Source: Pal, 2021*

Low GRADE	The evidence suggests that Cabozantinib results in little to no difference in **overall survival** when compared with sunitinib in patient population with metastatic papillary renal cell carcinoma. *Source: Pal, 2021*

No GRADE	No evidence was found regarding the effect of cabozantinib, crizotinib and savolitinib on **quality of life** when compared with sunitinib in patient with non clear cell RCC.

Low GRADE	The evidence suggests that Cabozantinib, crizotinib and savolitinib results in little to no difference in **complications** when compared with sunitinib in patient population with metastatic papillary renal cell carcinoma.

	Source: Pal, 2021

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er werden één systematische review en 3 RCT's gevonden die rapporteerden over de uitkomstmaten van progressievrije overleving, overall survival, kwaliteit van leven en complicaties.

In de studies werden vier verschillende vergelijkingen (everolimus versus sunitinib; Temsirolimus vs sunitinib; Savolitinib vs sunitinib; Cabozantinib, crizotinib and savolitinib vs sunitinib) gerapporteerd met betrekking tot de uitkomstmaten. Het bewijsniveau met betrekking tot everolimus versus sunitinib was matig en voor de rest van de vergelijkingen laag.

Zelfs zonder verdere onderverdeling in verschillende histologische subtypes is de mate van bewijsvoering matig tot zelfs laag. Op basis van survival overwegingen (OS en/of PFS) lijkt sunitinib de voorkeur te hebben boven een mTOR remmer zoals naar voren komt in de systematic review van Osterman.

De studies van Pal en Choueri hebben beide gekeken naar patiënten met een tumor van het papillaire subtype, waarbij de laatste studie zich beperkt heeft tot de MET gedreven papillaire niercelcarcinomen.

Als er gekeken wordt naar de studie waarbij alleen papillaire histologie werd toegestaan dan lijkt cabozantinib superieur aan sunitib als het gaat om progressie vrije overleving. Een positief effect op OS heeft deze fase II studie niet kunnen aan tonen bij de analyse van 152 patienten.

Van de savolitinib studie van Choueiri is het wachten op een update van de gegevens. Op basis van de huidige gegevens is er geen plek voor savolitinib.

Onlangs zijn er twee fase 2-onderzoeken uitgevoerd naar Pembrolizumab in combinatie met Lenvatinib en Nivolumab in combinatie met Cabozantinib als eerstelijnsbehandeling voor gevorderd niet-heldercellig niercelcarcinoom (Albiges, 2023). Omdat dit onderzoek beschikbaar is gekomen na het verrichten van de literatuuur analyse laat het proces van opstellen van de richtlijn geen ruimte voor volledig opnemen van deze gegevens. Hoe de optie pembrolizumab + lenvatinib zich verhoudt tot monotherapie TKI zal onderwerp van discussie kunnen zijn in de Medische Inhoudelijke Standpuntgroep (MIS-groep) van de landelijke tumorwerkgroep (DRCG). De studie met Pembrolizumab en Lenvatinib (Keynote B61: Albiges, 2023) heeft aanvullend bewijs geleverd over de werkzaamheid en veiligheid van deze behandeling bij deze specifieke groep patiënten. Een aanzienlijk percentage van de patiënten (49%) vertoonde een bevestigde objectieve respons, waaronder complete en gedeeltelijke responsen. De combinatie van pembrolizumab en lenvatinib toonde antitumoractiviteit bij gevorderd niet-heldercellig niercelcarcinoom. Hoewel enkele bijwerkingen werden waargenomen, waren er geen nieuwe veiligheidssignalen. Ongeveer de helft van de patiënten (51%) ervoer graad 3-4 behandelingsgerelateerde bijwerkingen, zoals hypertensie, proteïnurie en stomatitis. Hoewel de activiteit en veiligheid van deze behandeling zijn aangetoond, zijn verdere langetermijnresultaten en onderzoek noodzakelijk om een volledig begrip te krijgen van de effectiviteit en veiligheid van deze combinatie. Daarnaast includeerde de cabozantinib- en nivolumabstudie 40 patiënten met papillaire en niet-geclassificeerde RCC met een responspercentage van 47% en een PFS van 13 (7-16) maanden (Lee, 2022). In deze studie werd chromofoob RCC uitgesloten en was het percentage papRCC 68%. Indirecte vergelijkingen suggereren dat deze gegevens vergelijkbaar zijn met een verhoogde werkzaamheid met die van VEGFR-TKI monotherapie (Lee, 2022).

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Gezien de beperkte opties, overwegen patiënten vooral of de aangetoonde meerwaarde ten opzichte van de bekende bijwerkingen van sunitinib voldoende is om deze therapie te ondergaan. In het geval van een gemetastaseerd papillair niercelcarcinoom zijn zowel sunitinib als cabozantinib mogelijkheden. Deze keuze moet samen met de patiënt worden afgewogen tegen de bijwerkingen van beide TKI's. Het bijwerkingenpatroon van beide TKI's komt overeen met de uitgebreidere gegevens die we kennen bij gemetastaseerd heldercellig niercelcarcinoom. Hoewel de effectiviteit van cabozantinib lijkt toe te nemen, zoals blijkt uit een betere PFS, lijkt ook de toxiciteit groter te zijn.

Kosten (middelenbeslag)
Voor de meeste histologische subtypes van het niet-heldercellige niereclcarcinoom is er dus één eerstelijns optie en dat is sunitinib.
Voor patienten met een gemetastaseerd papillair niercelcarcinoom moet (als er gekozen wordt voor therapie) de afweging gemaakt worden tussen sunitinib en cabozantinib. Sunitinib is inmiddels van patent af en heeft daarom een evidente andere impact op kosten dan cabozantinib. Daarbij lijkt het bijwerkingenpatroon van sunitinib gunstiger dan dat van cabozantinib. Dit zal mee genomen moeten worden in de afweging tegen signalen van hogere effectiviteit die zich (nog) niet vertaald hebben in een langere overleving.

Aanvaardbaarheid, haalbaarheid en implementatie
Sunitinib wordt momenteel als de standaard behandeling gezien. De waarde van cabozantinib bij het niet-heldercellig niercelcarcinoom is nog niet eerder opgenomen in de Nederlandse Richtlijn, maar is wel toepasbaar.

Zeer binnenkort worden data van meerdere studies verwacht mbt rol van immunotherapie . Een hoopvol signaal is gezien in de fase 2 studie met permbrolizumab in combinatie met lenvatinib

Aanbeveling

Bespreek palliatieve behandeling met sunitinib bij een patiënt met een gemetastaseerd niet-heldercellig niercelcarcinoom als patient in afdoende conditie is voor palliatieve systeemtherapie.

Maak bij patiënten met een gemetastaseerd papilliar niercelcarcinoom de afweging of er een meerwaarde is van cabozantinib boven sunitinib als er palliatieve systemische therapie gestart gaat worden.

Kennislacunes
Geen.

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Module 4 Oligometastasering

Uitgangsvraag
Wat is de rol van lokale behandeling (chirurgische metastasectomie, SBRT, ablatieve technieken) bij patiënten met a) synchrone oligometastasen / b) metachrone oligometastasen?

Inleiding
Voor patiënten met oligometastasen (≤5 in ≤2 organen) kan zowel in de synchrone als in de metachrone setting, definitieve metastase-gerichte lokale therapie aangeboden worden zoals een metastasectomie, ablatieve therapie zoals RFA, cryo- of microwave ablatie (MWA) als ook hooggedoseerde radiotherapie (stereotactische ablatieve radiotherapie, SABR). Het is onduidelijk wat de optimale timing is van inzet van een van deze lokaal ablatieve behandelingen. Ook is niet duidelijk welke therapie het beste ingezet kan worden, die mogelijk afhankelijk is van de locatie van de metastasen. Het doel van definitieve metastase-gerichte lokale therapie kan zijn: langdurige (lokale) ziekte controle waarbij curatie de intentie kan zijn, of uitstel van systemische behandeling of uitstel van switch naar een tweede lijn systemische behandeling, echter het effect hiervan op overleving is nog niet duidelijk.
We houden hierbij aan dat synchrone oligometastasen zijn ontstaan binnen 6 maanden na diagnose van de primaire tumor en metachrone oligometastasen 6 maanden na diagnose van de primaire tumor zijn ontstaan, zonder het geven van systemische behandeling in die periode. Van oligoprogressieve ziekte is sprake als er groei of opnieuw groei is van een metastase onder systemische behandeling.

Search and select
A systematic review of the literature was performed to answer the following question:

P: patients	patients with renal cell carcinoma and a) synchronous- / b) metachronous oligometastatic disease
I: intervention	ablation, (stereotactic) radiotherapy, metastasectomy
C: control	no or incomplete removal/treatment
O: outcome measure	disease-free survival, overall survival, quality of life, complications, postponement of systemic therapy

<u>Relevant outcome measures</u>
The guideline development group considered disease-free survival and overall survival as critical outcome measures for decision making; and quality of life, complications, and postponement of systemic therapy as important outcome measures for decision making.

A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

The working group defined a relative risk (RR) or hazard ratio (HR) <0.80 or >1.25 as a minimal clinically (patient) important difference for dichotomous or survival variables, and >0.5 SD for continuous variables.

<u>Search and select (Methods)</u>
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until April 12th 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 1094 hits. Studies that

met the following criteria were eligible for selection: studies reporting original data, systematic reviews, randomized controlled trials (RCTs) and observational comparative studies reporting on ablation, (stereotactic) radiotherapy or metastasectomy with no or incomplete removal in patients with renal cell carcinoma and synchronous oligometastases or metachronous metastases. Twenty-eight studies were initially selected based on title and abstract screening. After reading the full text, nineteen studies were excluded (see the table with reasons for exclusion under the tab Methods), and nine studies (1 systematic review containing 8 observational studies and 8 other observational studies) were included.

Results

Nine studies were included in the analysis of the literature. One systematic review was included (Hsieh, 2021). Since the systematic review was of poor quality, the eight suitable studies were individually included in the literature analysis (Alt, 2011; Ishihara, 2020; Kwak, 2007; Li, 2018; Russo, 2007; Sun, 2018; You, 2016; Yu, 2015). All these studies examined the effect of metastasectomy. Besides, eight observational studies were included (Dragomir, 2020; Fares, 2019; Kim, 2019; Liu, 2021; Shin, 2021; Suzuki, 2021; Thomas, 2016; Tornberg, 2018). Seven of these studies examined the effect of metastasectomy and one study was about (stereotactic) radiotherapy. No studies about ablation were included.
A subgroup analysis was performed on studies that reported data about synchronous and metachronous metastases separately. In addition, in some studies, patients received additional treatment with targeted therapy or immunotherapy, which were also analyzed as a subgroup. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

The module is structured as follows:

1. Metastasectomy
    - No subgroup
    - Subgroup about synchronous and metachronous metastases
    - Subgroup about additional use of targeted therapy or immunotherapy
2. (stereotactic) radiotherapy
    - Subgroup about additional use of target therapy or immunotherapy

1. Metastasectomy

Summary of literature

Description of studies

Kwak (2007) performed a retrospective study to determine the efficacy of metastasectomy after nephrectomy in patient with metastatic renal cell carcinoma who had not received systemic therapy. Patients who had not undergone radical nephrectomy or metastasectomy was incomplete were excluded. In total, 21 patients received metastasectomy and 41 patients did not receive metastasectomy. Groups were not comparable. Patients in the non-metastasectomy group had a higher ECOG performance status, had more poor prognostic factors, and had more multiple metastases. The outcome of interest was overall survival.

Russo (2007) performed a retrospective study to examine the effect of cytoreductive nephrectomy alone or in conjunction with nephrectomy and complete metastasectomy. It was not reported whether these patients received prior immunotherapy or whether they were naieve to systemic treatment. 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 were included. In total, 61 patients had removal of the kidney and all metastatic sites (nephrectomy/complete metastasectomy), and 30 patients

had cytoreductive nephrectomy alone without resection of all metastatic sites. It is unclear if groups were comparable, since patient characteristics were not reported separately for both groups. The outcome of interest was overall survival.

Results

1. Disease-free survival
   Not reported.

2. Overall survival
   Kwak (2007) reported that patients who received metastasectomy had a median overall survival of 36.5 months (range: 4.0 to 182.7 months) as compared to 8.4 months (range: 0.9 to 63.7 months) for patients who did not undergo metastasectomy (p<0.001).

   Russo (2007) reported that patients who underwent complete metastasectomy had a median overall survival of 30 months as compared to 12 months for patients who had incomplete or no metastasectomy.

3. Quality of life
   Not reported.

4. Complications
   Not reported.

5. Postponement of systemic therapy
   Not reported.

Level of evidence of the literature
According to GRADE, the level of evidence of observational studies starts at low.

The level of evidence regarding the outcome measure **overall survival** was downgraded to very low because of limitations regarding the study design (-1, risk of bias; groups most likely not comparable) and the optimal information size was not achieved (-1, imprecision).

The level of evidence regarding the outcome measures **disease-free survival, quality of life, complications** and **postponement of systemic therapy** could not be assessed with GRADE since it was not reported in the included studies.

Conclusions

Very low GRADE	The evidence is very uncertain about the effect of metastasectomy on **overall survival** when compared with no or incomplete removal in patients with renal cell carcinoma and synchronous oligometastases and metachronous metastases. *Source: Kwak, 2007; Russo, 2007*

No GRADE	No evidence was found regarding the effect of metastasectomy on **disease-free survival, quality of life, complications,** and **postponement of systemic therapy** when compared with no or incomplete removal in patients with

	renal cell carcinoma and synchronous oligometastases and metachronous metastases.

Subgroup: synchronous and metachronous metastatic renal cell carcinoma
Results reported separately for these subgroups
Patient population might have additional use of targeted therapy/immunotherapy

Summary of literature

Description of studies

Shin (2020) performed a retrospective study to analyze and identify prognostic factors for survival of metastatic renal cell carcinoma to the pancreas (PM-RCC) with a focus on the role of surgical resection on the prognosis. Patients who had PM-RCC at first mRCC diagnosis or at the initiation of first-line systemic therapy were included and patients with RCC involvement in the pancreas by disease progression following the first-line therapy and beyond were excluded. In this study, patients from both before and after introduction of the tyrosine kinase inhibitors were included. In total, 104 patients had synchronous PM-RCC of which 24 patients received no surgery, 14 patients received only nephrectomy and 66 patients received both nephrectomy and metastasectomy. Groups were not comparable. Patients who received metastasectomy were younger and had less diabetes mellitus, while patients who received no surgery had a higher T stage. Besides, 196 patients had metachronous PM-RCC of which 64 patients had no metastasectomy and 132 patients had a metastasectomy. Groups were not comparable. Patients who received metastasectomy were younger and had less diabetes mellitus but a higher nuclear grade. The outcome of interest was overall survival.

Thomas (2016) performed a retrospective study to determine whether metastasectomy has any survival benefit in patients with metastatic renal cell carcinoma with sarcomatoid dedifferentiation (sRCC) treated with radical nephrectomy. Patients with RCC and sarcomatoid features with nephrectomy were included. Exclusion criteria were patients diagnosed with sRCC subsequent to nephrectomy (i.e., at time of metastasectomy), with no metastatic disease, with sarcomatoid percentage of 100%, in unreported clinical trials, with history of other metastatic malignancy, or with incomplete follow-up information. It was not reported whether these patients received immunotherapy prior or whether they were naieve to systemic treatment. In total, of patients with synchronous metastasis at diagnosis, 30 patients underwent metastasectomy and 26 patients had no metastasectomy. Groups were not comparable. Patients who received metastasectomy had a lower percentage of sarcomatoid component in sRCC. For patients with asynchronous metastasis at diagnosis, 10 patients underwent metastasectomy and 14 patients had no metastasectomy. Groups were not comparable. Patients in the no-metastasectomy group had a higher BMI and all received systemic therapy at any time. The outcome of interest was overall survival.

Results

Synchronous metastases

1. Disease-free survival
   Not reported.

2. Overall survival
   Shin (2020) reported that the median overall survival for synchronous PM-RCC was 23.7 months (range: 12.2 to 59.3 months) for patients who received metastasectomy and nephrectomy, 18.1 months (range: 9.3 to 69.5 months) for patients who received only nephrectomy, and 16.8 months (range: 8.8 to 25.1 months) for patients who received no surgery (p=0.121).

Thomas (2016) reported the overall survival for synchronous sRCC was 8.4 months for patients who received metastasectomy and 8.0 months for patients who had no metastasectomy (p=0.35)

3. Quality of life
   Not reported.

4. Complications
   Not reported.
5. Postponement of systemic therapy
   Not reported.

Metachronous metastases

1. Disease-free survival
   Not reported.

2. Overall survival
   Shin (2020) reported that the median overall survival for metachronous PM-RCC was 53.7 months (range: 25.3 to 83.4 months) for patients who received metastasectomy as compared to 45.1 months (range: 20.4 to 67.8 months) for patients who received no metastasectomy (p=0.012).

   Thomas (2016) reported that the overall survival for asynchronous sRCC was 36.2 months for patients who received metastasectomy as compared to 13.7 months for patients who had no metastasectomy (p=0.29).

3. Quality of life
   Not reported.

4. Complications
   Not reported.

5. Postponement of systemic therapy
   Not reported.

Level of evidence of the literature
According to GRADE, the level of evidence of observational studies start at low.

Synchronous oligometastases
The level of evidence regarding the outcome measure **overall survival** was downgraded to very low because of limitations regarding the study design (-1, risk of bias) and the optimal information size was not achieved (-1, imprecision).

The level of evidence regarding the outcome measures **disease-free survival, quality of life, complications** and **postponement of systemic therapy** could not be assessed with GRADE since it was not reported in the included studies.

Metachronous metastases
The level of evidence regarding the outcome measure **overall survival** was downgraded to very low because of limitations regarding the study design (-1, risk of bias) and the optimal information size was not achieved (-1, imprecision).

The level of evidence regarding the outcome measures **disease-free survival, quality of life, complications** and **postponement of systemic therapy** could not be assessed with GRADE since it was not reported in the included studies.

Conclusions

Synchronous metastases

Very low GRADE	The evidence is very uncertain about the effect of metastasectomy on **overall survival** when compared with no or incomplete removal in patients with renal cell carcinoma and synchronous oligometastases. *Source: Shin, 2020; Thomas, 2016*

No GRADE	No evidence was found regarding the effect of metastasectomy on **disease-free survival, quality of life, complications,** and **postponement of systemic therapy** when compared with no or incomplete removal in patients with renal cell carcinoma and synchronous oligometastases.

Metachronous metastases

Very low GRADE	The evidence is very uncertain about the effect of metastasectomy on **overall survival** when compared with no or incomplete removal in patients with renal cell carcinoma and metachronous metastases. *Source: Shin, 2020; Thomas, 2016*

No GRADE	No evidence was found regarding the effect of metastasectomy on **disease-free survival, quality of life, complications,** and **postponement of systemic therapy** when compared with no or incomplete removal in patients with renal cell carcinoma and metachronous metastases.

Subgroup: additional use of targeted therapy/immunotherapy
Patient population consists of both synchronous and metachronous renal cell carcinoma metastases (data not reported for these subgroups separately)

Summary of literature

Dragomir (2020) performed a retrospective study to assess the impact of complete metastasectomy in metastatic renal cell carcinoma (mRCC). Patients diagnosed with mRCC with prior nephrectomy were included, while patients receiving a first incomplete metastasectomy were excluded. 12% of the patients had first-line targeted treatment prior to matching date. No subanalysis was performed for this group. In total, 229 patients underwent complete metastasectomy (28.8% with synchronous metastases) and were matched with 803 patients not treated with metastasectomy (30.4% with synchronous metastases). Besides, these patients were matched on specific variables such as the usage of first-line targeted treatment. Groups were comparable at baseline after matching. The outcome of interest was overall survival and time to first-line targeted treatment.

Fares (2019) performed a propensity score-matched analysis to determine overall survival benefit of complete metastasectomy (CM) in metastatic renal cell carcinoma (mRCC). Patients with clear cell histology and absence of sarcomatoid or rhabdoid features who underwent previous nephrectomy. Besides, patients who underwent CM and patients treated without metastasectomy and with targeted therapy alone who fit inclusion criteria were included. No subgroup analysis was performed for the targeted therapy group. In total, 37 patients underwent CM (37% with synchronous metastases) and 37 patients had no metastasectomy (19% with synchronous metastases). Groups were not comparable. All patients who did not underwent metastasectomy had systemic therapy at first line as compared to 25 of the 37 patients (68%) who underwent CM. The outcome of interest was overall survival.

Ishihara (2020) performed a retrospective study to determine survival following metastasectomy for renal cell carcinoma (RCC) in the postcytokine therapy era. Patients diagnosed with metastatic RCC (mRCC) were included. Exclusion criteria were those who were registered on clinical trials, those who had undergone maintenance dialysis, those who had a kidney transplant, those who were administered first-line ipilimumab and nivolumab as systematic therapy and those with missing eligible data. In total, 45 patients underwent complete metastasectomy (cMS; 17.8% with synchronous metastases), 53 patients underwent incomplete metastasectomy (icMS; 50.9% with synchronous metastases), and 216 patients had no metastasectomy (nonMS; 58.3% with synchronous metastases). Groups were not comparable. These three groups were different in age (nonMS group was older), the frequency of sarcomatoid differentiation (nonMS group had higher frequency), IMDC risk (nonMS group had more often a poor risk), frequency of prior nephrectomy (nonMS group had less often prior nephrectomy), metastasis status (nonMS group more synchronous metastases), frequency of systemic therapy (cMS group lower frequency) and follow-up (nonMS group had a lower follow-up period). The outcome of interest was overall survival.

Kim (2019) performed a retrospective study to determine the effects of metastasectomy to those of non-metastasectomy regarding overall survival and progression-free survival in metastatic renal cell carcinoma (mRCC). Exclusion criteria were a non-complete history of survival outcomes in the National Cancer Registry Database, non-complete surgical records concerning metastasectomy or nephrectomy, or age <19 years. In total, 83 patients underwent metastasectomy (44.6% with synchronous metastases) and 190 patients had no metastasectomy (65.3% with synchronous metastases). The choice of targeted agents was

at the discretion of the treating urologist (JC) according to each patient's pathology and coverage by the Health Insurance. It was not reported how many patients received targeted therapy, which targeted therapy and whether this was prior or after the metastasectomy. Groups were not comparable. Patients in the metastasectomy group were younger, had a lower clinical T stage, had a higher rate of favorable- and intermediate-risk groups, and had less synchronous metastases. In addition, patients in the metastasectomy group had a higher rate of bone, brain, and pancreas metastases and a lower rate of liver metastases and received more often cytoreductive nephrectomy and radiation therapy than patients in the non-metastasectomy group. The outcome of interest was overall survival.

Li (2018) performed a retrospective chart-review analysis to assess the clinical impact of local interventions after receiving targeted therapies. Consecutive metastatic renal cell carcinoma patients who had received at least one line of targeted treatment were included. Exclusion criteria were incomplete data or loss of follow-up. In total, 26 patients received complete resection, 23 patients underwent incomplete resection, and 75 patients did not receive metastasectomy. Seventy-five patients (60.5%) received targeted therapies only, twenty-six patients received complete resection, while the final 23 received incomplete local interventions for their metastatic lesions. Groups were not comparable. Patients who only received targeted therapy had a higher percentage of poor MSKCC risk, had more often more than one metastatic site, and had a shorter targeted treatment duration and median follow-up. The outcome of interest was overall survival.

Sun (2018) performed a retrospective study to determine the use of metastasectomy for metastatic renal cell carcinoma (mRCC) at diagnosis in the targeted therapy era. All patients >18 years old with a primary diagnosis of mRCC who underwent a cytoreductive nephrectomy were included. Some of the included patients received targeted therapy. It was not reported how many patients received targeted therapy, which targeted therapy and whether this was prior or after the metastasectomy. Post-propensity matched survival analyses were performed. In total, 1695 patients who underwent metastasectomy were matched to 1695 patients who did not receive metastasectomy. Groups were comparable. The outcome of interest was overall survival.

Suzuki (2022) performed a retrospective study to determine the therapeutic efficacy of surgical metastasectomy in patients with solitary metastasis of renal cell carcinoma (RCC). Patients with a history of nephrectomy for primary site of RCC who had been treated for solitary metastasis of RCC were included. Some of the included patients received targeted therapy. It was not reported how many patients received targeted therapy, which targeted therapy and whether this was prior or after the metastasectomy. In total, 29 patients underwent surgical metastasectomy and 44 patients did not undergo metastasectomy. Groups were not comparable. The duration from primary nephrectomy to occurrence of metastasis was shorter for patients who did not undergo metastasectomy. Besides, 11 of the 18 patients who underwent metastasectomy had systemic therapy prior to the metastasectomy, while it is unclear whether patients who did not undergo metastasectomy received any systemic therapy. The outcome of interest was overall survival.

Tornberg (2018) performed a retrospective study to determine the outcome of metastasectomy in mRCC in the era of targeted therapies as a primary endpoint. Patients with sporadic mRCC treated by surgery for adrenal or lymph node metastases and whose primary tumor was inevitably treated by surgery were included. In addition, patients treated by either radical or cytoreductive intention in the initial operation, nephrectomy or

nephrectomy combined with simultaneous metastasectomy for RCC were included. Exclusion criteria were patients who received palliative treatment alone for metastases and patients with coincidentally encountered lymph node involvement or minimal findings in the adrenal gland. In total, 46 patients underwent complete metastasectomy and 51 patients underwent non-complete metastasectomy. Besides, systemic treatment was administered in both groups. A medical oncologist was consulted regarding the suitability of targeted therapies when a relapse without any reasonable prospect of surgical treatment was observed. 55 patients underwent first line therapy, and 43 underwent second line therapy. It was not reported whether this targeted therapy was prior or after the metastasectomy. It is unclear if groups were comparable, since no patient characteristics were reported for both groups separately. The outcome of interest was postponement of systemic therapy.

You (2016) performed a retrospective study to assess the value of metastasectomy in patients treated with targeted therapy for metastatic renal cell carcinoma (mRCC). Patients with mRCC without prior systemic therapy were included, while patients who underwent consolidation metastasectomy after targeted therapy were excluded. It was not reported whether these patients received targeted therapy prior or whether they were naieve to systemic treatment. In total, 33 patient underwent complete metastasectomy (cMS; 15.2% with synchronous metastases), 29 patients received incomplete metastasectomy (icMS; 51.7% with synchronous metastases)
and 263 patients did not receive metastasectomy (nonMS; 60.8% with synchronous metastases). Groups were comparable, except for age (nonMS patients were older), history of nephrectomy (cMS patients all received nephrectomy), type of metastasis (nonMS patients had more synchronous metastases), IMDC risk groups (cMS patients had more favorable risk), histology (nonMS patients had more non-clear cell histology), and bone metastases (cMS patients had less bone metastases). The outcome of interest was overall survival.

Yu (2015) performed a retrospective study to determine the efficacy of surgery in the treatment of metastatic renal cell carcinoma (mRCC). Patients diagnosed with metastatic renal cell carcinoma who had oligometastasis and a Karnofsky Performance Scale not less than 80 were included. Exclusion criteria were no previous nephrectomy, incomplete data concerning survival time, pathology, metastatic sites, and detailed record of surgery. In total, 31 patients received complete metastasectomy, 11 patients received incomplete metastasectomy and 54 patients did not receive metastasectomy. It was not reported whether these patients received targeted therapy prior or whether they were naieve to systemic treatment. Groups were comparable except that patients who received metastasectomy had more often only one metastatic organ. The outcome of interest was overall survival.

Results

1. Disease-free survival
   Not reported.

2. Overall survival
   Ten studies reported overall survival (table 1). When survival was expressed in years, this was converted into months.

   Table 1. Overview of studies reporting overall survival (in months).

Study	Metastasectomy	No or incomplete resection	P-value and HR (if reported)
Dragomir, 2020	81 months (IQR: 58 to NR) (n=229)	61 months (IQR: 26 to NR) (n=803)	-
Fares, 2019	98.3 months (n=37)	40.5 months (n=37)	HR=0.24, 95%CI 0.11 to 0.53 p< 0.0001
Ishihara, 2020	NR (121.9 to NR) (n=45)	No: 28.1 months (22.6 to 41.5) (n=216) Incomplete: 81.5 months (44.6 to NR) (n=53)	P<0.0001
Kim, 2019	32.0 months (n=83)	12.8 months (n=190)	P<0.001
Li, 2018	60.6 months (n=26)	No: 42 months Incomplete: 28.8 months (n=75)	p=0.024
Sun, 2018	24.1 months (n=1695)	18.9 months (n=1695)	p<0.001
Suzuki, 2022	NR (n=29)	62.9 months (n=44)	P=0.002
You, 2016	92.5 months (n=33)	No: 23.5 months (n=263) Incomplete: 29.6 months (n=29)	P<0.001
Yu, 2015	52 months (95% CI: 26.8 to 77.2) (n=31)	No: 22 months (95% CI: 17.6–26.4) (n=54) Incomplete: 16 months (95% CI: 9.5 to 22.5) (n=11)	P=0.001

Abbreviations: HR=hazard ratio; IQR=Interquartile range; NR=not reached.

3. Quality of life
   Not reported.

4. Complications
   Suzuki (2022) reported perioperative complications. No serious perioperative complications were demonstrated for patients who underwent surgical metastasectomy.

5. Postponement of systemic therapy
   Dragomir (2020) reported that patients without prior exposure to systemic therapy had a median time to first-line targeted treatment during follow-up of 49 months (IQR: 14 to NR) and 38 months (IQR: 11 to 66) for patients receiving complete metastasectomy and patients not treated with metastasectomy, respectively (p=0.0057).

   Tornberg (2018) reported time from diagnosis to oncological treatment. For patients with non-complete metastasectomy the median interval was 19 months (IQR: 1-71 months), while this was not achieved for patients with complete metastasectomy.

Level of evidence of the literature
According to GRADE, the level of evidence of observational studies start at low.

The level of evidence regarding the outcome measure **overall survival** was downgraded to very low because of limitations regarding the study design (-1, risk of bias) and the indirectness (-1, variation in patient population between studies, thus pooling of data not possible).

The level of evidence regarding the outcome measure **complications** was downgraded to very low because of limitations regarding the study design (-1, risk of bias) and the indirectness (-1, variation in patient population between studies, thus pooling of data not possible).

The level of evidence regarding the outcome measure **postponement of systemic therapy** was downgraded to very low because of limitations regarding the study design (-1, risk of bias) and the optimal information size was not achieved (-1, imprecision).

The level of evidence regarding the outcome measures **disease-free survival** and **quality of life** could not be assessed with GRADE since it was not reported in the included studies.

Conclusions

Very low GRADE	The evidence is very uncertain about the effect of metastasectomy (with targeted therapy/immunotherapy) on **overall survival** when compared with no or incomplete removal (and targeted therapy/immunotherapy) in patients with renal cell carcinoma and synchronous oligometastases and metachronous metastases. *Source: Dragomir, 2020; Ishihara, 2020; Kim, 2019; Li, 2018; Sun, 2018; Suzuki, 2022; You, 2016; Yu, 2015*

Very low GRADE	The evidence is very uncertain about the effect of metastasectomy (with targeted therapy/immunotherapy) on **complications** when compared with no or incomplete removal (and targeted therapy/immunotherapy) in patients with renal cell carcinoma and synchronous oligometastases and metachronous metastases. *Source: Suzuki, 2022*

Very low GRADE	The evidence is very uncertain about the effect of metastasectomy (with targeted therapy/immunotherapy) on **postponement of systemic therapy** when compared with no or incomplete removal (and targeted therapy/immunotherapy) in patients with renal cell carcinoma and synchronous oligometastases and metachronous metastases. *Source: Dragomir, 2020; Tornberg, 2018*

No GRADE	No evidence was found regarding the effect of metastasectomy (with targeted therapy/immunotherapy) on **disease-free survival** and **quality of life** when compared with no or incomplete removal (and targeted therapy/ immunotherapy) in patients with renal cell carcinoma and synchronous oligometastases and metachronous metastases.

2. (stereotactic) radiotherapy

Subgroup: additional use of targeted therapy/immunotherapy
Patient population consists of both synchronous and metachronous renal cell carcinoma metastases (data not reported for these subgroups separately)

Summary of literature

Description of studies

Liu (2021) performed a retrospective study to determine the survival outcomes of patients receiving stereotactic body radiation therapy (SBRT) plus tyrosine kinase inhibitors (TKIs) versus TKIs alone. Patients aged ≥ 18 years who received TKI treatment for metastatic renal cell carcinoma were included. Exclusion criteria were patients treated with conventionally fractionated radiotherapy or received immunotherapy as first-line treatment. In total, 85 patients received SBRT and TKI (48.2% with synchronous metastasis) and 105 patients received TKI alone (53.3% with synchronous metastasis). Groups were comparable except that patients who received SBRT and TKI were older and more likely to have bone metastases. The outcome of interest was overall survival.

Results

1. Disease-free survival
   Not reported.

2. Overall survival
   Liu (2021) reported that patients who received stereotactic radiotherapy and tyrosine kinase inhibitors had a median overall survival of 63.2 months as compared to 29.8 months for patients who received tyrosine kinase inhibitors alone (p<0.001).

3. Quality of life
   Not reported.

4. Complications
   Not reported.

5. Postponement of systemic therapy
   Not reported.

Level of evidence of the literature

According to GRADE, the level of evidence of observational studies start at low.

The level of evidence regarding the outcome measure **overall survival** was downgraded to very low because of limitations regarding the study design (-1, risk of bias) and the optimal information size was not achieved (-1, imprecision).

The level of evidence regarding the outcome measures **disease-free survival, quality of life, complications** and **postponement of systemic therapy** could not be assessed with GRADE since it was not reported in the included studies.

Conclusions

Very low GRADE	The evidence is very uncertain about the effect of stereotactic radiation therapy (with tyrosine kinase inhibitors) on **overall survival** when compared with no or incomplete removal (and tyrosine kinase inhibitors) in patients with renal cell carcinoma and synchronous oligometastases and metachronous metastases. *Source: Liu, 2021*

No GRADE	No evidence was found regarding the effect of stereotactic radiation therapy (with tyrosine kinase inhibitors) on **disease-free survival, quality of life, complications,** and **postponement of systemic therapy** when compared with no or incomplete removal (and tyrosine kinase inhibitors) on patients with renal cell carcinoma and synchronous oligometastases and metachronous metastases.

Overwegingen – van bewijs naar aanbeveling

<u>Voor- en nadelen van de interventie en de kwaliteit van het bewijs</u>

De werkgroep heeft een literatuurstudie verricht naar welke behandeling (metastasectomie, SBRT/SABR, ablatieve therapie) het beste kan worden toegepast bij patiënten met synchrone oligometastasen / metachrone oligometastasen.

1. Metastasectomie

Er werd één systematische review (Hsieh, 2021) gevonden met daarin acht relevante observationele studies over het effect van metastasectomy (Alt, 2011; Ishihara, 2020; Kwak, 2007; Li, 2018; Russo, 2007; Sun, 2018; You, 2016; Yu, 2015). Daarnaast werden er nog zeven andere observationele studies over metastasectomy gevonden (Dragomir, 2020; Fares, 2019; Kim, 2019; Shin, 2021; Suzuki, 2021; Thomas, 2016; Tornberg, 2018).
De bewijskracht voor de cruciale uitkomstmaat 'overall survival' werd beoordeeld als zeer laag vanwege methodologische beperkingen door de retrospectieve studie opzet en heterogeniteit tussen de studies. Voor de cruciale uitkomstmaat 'ziektevrije overleving' werd geen bewijs gevonden. Dit leidt tot een zeer lage overall bewijskracht. Ook voor de belangrijke uitkomstmaten 'kwaliteit van leven', 'complicaties' en 'uitstel van systeemtherapie' werd geen bewijs gevonden of was de bewijskracht zeer laag door methodologische beperkingen en het lage aantal deelnemers. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten.

2. SBRT/SABR

Eén observationele studie over het effect van radiotherapie werd gevonden (Liu, 2021). De bewijskracht voor de cruciale uitkomstmaat 'overall survival' werd beoordeeld als zeer laag vanwege methodologische beperkingen door de retrospectieve studie opzet .Voor de cruciale uitkomstmaat 'ziektevrije overleving' en de belangrijke uitkomstmaten 'kwaliteit van leven',
'complicaties' en 'uitstel van systeemtherapie' werd geen bewijs gevonden. Dit leidt tot een zeer lage overall bewijskracht. Dit betekent dat andere studies kunnen leiden tot nieuwe inzichten.

Er kunnen op basis van alleen de literatuur geen sterke aanbevelingen geformuleerd worden over welke behandeling (metastasectomie, SABR, ablatie) het beste kan worden toegepast bij patiënten met synchrone oligometastasen / metachrone oligometastasen.

In de dagelijkse praktijk wordt SABR bij patienten met oligometasen met enige regelmaat toegepast, waarbij een reden kan zijn om systemische therapie uit te stellen. In twee prospectieve studies waarbij patienten werden behandeld met SABR in plaats van systemische therapie, resulteerde dit in een 1-jaars systemische therapie-vrije overleving van 82-91% (C. Tang, et al, Lancet Oncol, 2021 R. Hannan et al, European Urology Oncology 2022). Veiligheid van de behandeling werd bevestigd n de specifieke populatie van patiënten met oligometastasen ineen recente meta-analyse met goede resultaten voor wat betreft lokale controle van behandeling middels SABR (E.J. Lehrer, JAMA Oncol, 7 (2021). De SABR-ORCA meta-analyse rapporteerde over 28 studies en 623 patiënten met 2733 extracraniële metastasen van RCC behandeld met SABR, waarbij de lokale controle en OS na 1 jaar 89.1% en 86.8% respectievelijk, is. Behandeling—gerelateerde bijwerkingen waren minimaal met slechts 0.7% graad 3–4 bijwerkingen (N.G. Zaorsky, et al, Eur Urol Oncol, 2 (2019)). De grote beperking van deze meta-analyse is dat het een heterogene populatie betreft met oligometastatische, oligoprogressieve en polymetastastische patiënten die behandeld worden met SABR alleen, of gecombineerd met systemische therapie.

Het is belangrijk dat toekomstig onderzoek zich richt op de lange termijn uitkomsten van deze behandelmodaliteit, passende klinische parameters en biomarkers voor een betere patiënten selectie en fractioneringsschema's voor SABR.

Daarnaast is het belangrijk om de behandeling van oligometastasen middels metastatectomie en SABR ook uit te zetten tegen active surveillance (AS). In een recent gerapporteerde prospectieve observationele studie worden patiënten met een oligo-gemetastaseerd RCC die geen behandeling krijgen vergeleken met patiënten die direct starten met systemische behandeling. Resultaten laten zien dat in deze beschreven, geselecteerde groep, AS een veilig en gepast alternatief is voor het direct starten met systemische behandeling; een deel van deze patienten kreeg echter tijdens de AS ook metastase gerichte lokale behandeling. (Harrison, 2021).

Een prospectieve fase III studie is essentieel om de rol en waarde van SBRT/SABR en metastastactomie in de setting van oligo-gemetastaseerde patiënten te onderzoeken.
Er zijn geen studies gevonden over ablatie als behandelmogelijkheid van oligometastasen.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
De werkgroep heeft op grond van beschikbare literatuur geen verschil kunnen vinden tussen de behandeling middels metastatectomie en SABR voor oligo-gemetastaseerde ziekte voor wat betreft overleving. Verdere prospectief gerandomiseerde studies zijn nodig om het toegevoegde effect van lokale therapie (metastatectomie en SABR) te vergelijken met active surveillance of systemische therapie en om te identificeren welke patiënten hier het meeste voordeel van hebben. Hierbij is het ook belangrijk om patiënt gerapporteerde uitkomsten mee te nemen.

Als er sprake is van beperkte metastasen (1-5) dient men lokale behandeling te overwegen versus start met systemische behandeling of active surveillance. In de setting van één metastase bij patiënten in een goede conditie, waarbij nog geen weefsel bevestiging is voor wat betreft gemetastaseerde ziekte, heeft het vaak de voorkeur om een radicale metastatectomie te verrichten als de locatie dit toelaat. Bij patiënten in een goede conditie

met 2-5 metastasen dient eerder SABR overwogen te worden als niet invasieve behandeling in 1-5 sessies. Hierbij is het belangrijk mee te nemen dat bijwerkingen gerelateerd aan de behandeling beperkt zijn met een grote kans op lokale controle van de ziekte.

Als men behandeld wordt middels systemische therapie en er is sprake van oligoprogressieve ziekte, dat wil zeggen een metastase groeit of gaat weer groeien, kan
lokale behandeling overwogen worden met als doel uitstel van switch naar een tweede lijn systemische behandeling. Vaak wordt hierbij SABR overwogen, omdat dit een niet-invasieve behandeling is die niet, of kort de systemische behandeling onderbreekt.

Kosten (middelenbeslag)
De kosten effecten van metastatectomie, SABR en percutane ablaties zijn onvoldoende onderzocht. Ten opzichte van start met systemische behandeling is de verwachting dat lokale behandeling middels metastatectomie, SABR en percutane ablatie goedkoper is.

Aanvaardbaarheid, haalbaarheid en implementatie
Er zijn in Nederland enkele ziekenhuizen waar ervaring is met het uitvoeren van zowel metastatectomie en SABR. Ziekenhuizen die niet over deze ervaring of mogelijkheden beschikken dienen patiënten met oligo-gemetastaseerde ziekte te bespreken in een MDO met een centrum dat deze behandelingen aanbiedt, zodat voor alle patiënten een weloverwogen advies wordt geformuleerd waarbij langdurige (lokale) ziekte controle waarbij curatie de intentie kan zijn, of uitstel van systemische behandeling of uitstel van switch naar een tweede lijn systemische behandeling het uitgangspunt is en patiënten de kans krijgen om in expert centra behandeld te worden. Door patiënten te bespreken vindt er verspreiding van kennis plaats en wordt er meer naar eenduidig beleid gestreefd.

Aanbevelingen
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Het effect van zowel metastasectomie als stereotactische radiotherapie op overleving is vergeleken met geen/incomplete verwijdering of bestraling van oligometastasen erg onzeker. Het level of evidence is namelijk zeer laag. Over het effect op ziektevrije overleving, complicaties en uitstel van systemische therapie is geen uitspraak te doen door gebrek aan gegevens. Voor wat betreft ablatieve therapie is uberhaupt geen uitspraak te doen op basis van onvoldoende beschikbare literatuur. De rol die systemische therapie of immunotherapie hierbij speelt is tevens erg onzeker, hetgeen de plaatsbepaling en sequentie hiervan bemoeilijkt.

De keuze tussen metastatectomie, (percutane) ablatieve technieken zoals RFA, MWA, cryoablatie en SABR voor de behandeling van oligometastasen dient te worden gemaakt op basis van tumor karakteristieken (zoals aantal metastasen en locatie van de metastasen), patiëntenkarakteristieken (zoals conditie van de patiënt, co-morbiditeit), het moment van ontstaan van de metastasen en de voorkeur van de patiënt, waarbij afwachten of starten met systemische behandeling meegenomen moet worden.

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 wanneer dit een bijdrage kan leveren aan een curatieve behandeling en/of verlichting van klachten. Hierbij dient de conditie en comobiditeit van patient, localisatie van metastasen, aantal metastasen en lokale beschikbaarheid en expertise meegenomen te worden in de keuze voor behandeling en soort therapie.

Aanbeveling-subgroep metachrone oligometastasen

In subgroep analyse lijkt er mogelijk een voordeel in overleving voor metastasectomie in patienten met metachrone oligometastasen, echter is het level of evidence erg laag en daarmee het effect onzeker.

Overweeg metastasectomie bij patiënten met metachrone oligometastasen op basis van mogelijke overlevingswinst, klachtenverlichting 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.

Kennislacunes

P: patients	patients with renal cell carcinoma and a) synchronous- / b) metachronous oligometastatic disease
I: intervention	ablation, (stereotactic) radiotherapy, metastasectomy
C: control	no or incomplete removal/treatment
O: outcome measure	disease-free survival, overall survival, quality of life, complications, postponement of systemic therapy

Het is belangrijk dat toekomstig onderzoek zich richt op de lange termijn uitkomsten van SBRT/SABR, passende klinische parameters en biomarkers voor een betere patiënten selectie en fractioneringsschema's voor SBRT/SABR.

Daarnaast is het belangrijk om de behandeling van oligometastasen middels metastatectomie, percutane ablatie en SABR ook uit te zetten tegen active surveillance (AS).

Een prospectieve fase III studie is essentieel om de rol en waarde van SBRT/SABR en metastastactomie in de setting van oligo-gemetastaseerde patiënten te onderzoeken.

Het registeren van uitkomsten van de behandeling van SBRT/SABR in een landelijke registratie zouy kunnen bijdragen tot het oplossen van de kennislacune over de rol van SBRT/SABR bij de behandeling van patiënten met mRCC oligometastasen.

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Module 5 Cytoreductieve therapie gecombineerd met systemische therapie

Uitgangsvraag
Wat is de plaats van cytoreductieve therapie (cytoreductieve nefrectomie, embolisatie) naast systemische immuuntherapie bij patiënten met gemetastaseerd niercelcarcinoom?

Inleiding
In het tijdperk van TKIs (tyrosinekinaseremmers) is sunitinib behandeling niet-inferieur gebleken aan sunitinb+nefrectomie in intermediate/poor risk M+RCC (CARMENA, Méjean, 2018). Uitgestelde nefrectomie na sunitinib leidt niet tot betere PFS maar kan patiënten identificeren die resistent zijn voor systemische behandeling (SURTIME, Bex, 2019). In het huidige tijdperk van IO (immunotherapie) of combinatie therapie IO/TKI is de toegevoegde waarde van cytoreductieve tumornefrectomie onbekend en bestaat praktijkvariatie door verschillen in interpretatie van toepasbaarheid van voorgaande studieresultaten in de huidige tijd van combinatiebehandeling.

Search and select
A systematic review of the literature was performed to answer the following question:
What is the place of cytoreductive therapy in addition to systemic immunotherapy in patients with metastasized renal cell carcinoma?

P: patients	Patients with metastasized renal cell carcinoma
I: intervention	Cytoreductive nephrectomy or embolization and immuno combination therapy
C: control	Immuno combination therapy
O: outcome measure	1) Progression-free survival rate, 2) overall survival rate, 3) quality of life and 4) complications

<u>Relevant outcome measures</u>
The guideline development group considered progression-free survival rate and overall survival rate as a critical outcome measures for decision making; and quality of life and complications as important outcome measures for decision making.

The working group defined complications as follows: Clavien-Dindo classification, Common Toxicity Criteria.

The working group defined 20% as a minimal clinically (patient) important difference for PFS, treatment-free survival, for continuous outcomes: 0.5 SD.

<u>Search and select (Methods)</u>
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2017 until March 31st 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 281 hits. Studies that met the following criteria were eligible for selection: studies reporting original data, systematic reviews, randomized controlled trials (RCTs) and observational comparative studies reporting on cytoreductive nephrectomy (CN) or embolization in patients with metastasized renal cell carcinoma (mRCC). Twenty-nine studies were initially selected based on title and abstract screening. After reading the full text, 28 studies were excluded (see the table with reasons for exclusion under the tab Methods), and one study was included.

Results

One observational study (Singla, 2020) was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature

Description of studies

The American cohort study by Singla (2020) used the National Cancer Database with the objective to report survival outcomes in mRCC patients treated with CN combined with immunotherapy approaches versus immunotherapy alone. Renal cancer cases reported between 2015 and 2016 were eligible for inclusion and follow-up ranged from two to thirty-four months. To be included in the analysis, patients had to be metastatic at the time of diagnosis and receiving immunotherapy. Patients receiving any non-immuno systemic therapies and patients with a Charlson-Deyo comorbidity score >2 were excluded.

In total, the cohort consisted of 391 patients of which 221 patients were treated with CN + immunotherapy and 170 patients were treated with immunotherapy alone. Patients who received CN + immunotherapy were younger than those who received immunotherapy only, with a median (IQR) age of 57 years (51 to 64) and 64 years (57 to 72) respectively. At baseline, other demographic variables and Charlson-Deyo comorbidity score were similar between groups. Patients who underwent CN had a larger primary tumor size than those who did not (median (IQR) of 9.7 cm (7.4 to 12.0) compared to 8.0 cm (5.8 to 11.0) respectively). Overall survival (OS) was compared between the two groups, and uni- and multivariable analysis were used to identify predictors for worse OS (among patients diagnosed in 2015 only, n=185).

Results

1. Progression-free survival rate

The included literature did not report on this outcome measure.

2. Overall survival rate

The study by Singla (2021) determined overall survival in a subgroup of 185 out of the full sample consisting of 391 patients. This subgroup was diagnosed in 2015. The number of patients treated with CN + IO compared to IO only in this subgroup was not reported. Median OS was not reached in the CN + IO group, compared to 11.6 months (95% CI, 8.5 to 14.7) in the IO only group. Patients treated with CN + IO had better OS than those who received IO alone (unadjusted HR 0.23 (95% CI 0.15 to 0.37)) (p< 0.001). Multivariable analysis, adjusted for age, locally advanced cT stage, cN1 stage and the presence of bone, liver or brain metastases showed a HR of 0.22 (95% CI 0.11 to 0.42) (p= <0.001).

3. Quality of life

The included literature did not report on this outcome measure.

4. Complications

The included literature did not report on this outcome measure.

Level of evidence of the literature
Observational studies for therapeutic research questions start at low GRADE.

The level of evidence regarding the outcome measure **overall survival rate** was downgraded by two levels, one level because of study limitations (risk of bias) and one level because of the relatively small number of included patients (imprecision) to very low GRADE.

Due to lack of evidence, no grading was possible for the outcome measures **progression-free survival rate, quality of life** and **complications**.

Conclusions

No GRADE	The effect of cytoreductive nephrectomy combined with immunotherapy compared to immunotherapy only on **progression-free survival rate** in mRCC patients is unknown. The included literature did not report progression-free survival rate.

Very low GRADE	The evidence is very uncertain about the effect of cytoreductive nephrectomy combined with immunotherapy compared to immunotherapy only on **overall survival** in mRCC patients. *Source: Singla, 2021*

No GRADE	The effect of cytoreductive nephrectomy combined with immunotherapy compared to immunotherapy only on quality of life in mRCC patients is unknown. The included literature did not report on quality of life.

No GRADE	The effect of cytoreductive nephrectomy combined with immunotherapy compared to immunotherapy only on complications in mRCC patients is unknown. The included literature did not report on complications.

Overwegingen – van bewijs naar aanbeveling
Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is één observationele vergelijkende studie van lage kwaliteit gevonden die rapporteert over de uitkomstmaat overall survival. Er zijn geen studies gevonden die rapporteren over de uitkomstmaten progressie-vrije overleving, kwaliteit van leven en complicaties.
De patiënten die cytoreductieve therapie hebben gekregen naast immuuntherapie lijken een betere prognose te hebben dan patiënten die enkel immuuntherapie hebben gehad. Echter is de bewijskracht zeer laag, met name omdat er een groot risico is dat de groepen aan het begin van het onderzoek al een verschillende prognose hadden, hetgeen ertoe heeft bijgedragen dat voor deze behandeling (al dan niet cytoreductieve therapie) werd gekozen. Het is dus onzeker of het toepassen van cytoreductieve therapie bij alle patiënten met gemetastaseerd niercelcarcinoom van toegevoegde waarde zal zijn.
In twee gerandomiseerde fase 3 studies wordt de waarde van nefrectomie na immuuntherapie combinaties onderzocht (PROBE (Bell, 2022), NORDICSUN, (Lisager, 2014), maar het zal nog jaren duren voordat de studies compleet en de data beschikbaar zijn. Er zijn

verschillende niet vergelijkende retrospective studies waaruit geconcludeerd kan worden dat het bij bepaalde subgroepen te overwegen valt om een cytoreductieve nefrectomie uit te voeren na immuuntherapie (Fransen van de Putte, 2022; Meerveld-Eggink, 2022; Pignot, 2022; Singla, 2020). Lange-termijn data uit immuuntherapie combinatie studies laten zien dat patiënten met IMDC intermediate/poor risk – de klassieke risicogroep van patiënten met primair gemetastaseerd niercelcarcinoom – een mediane overleving hebben van 4 jaar. Na 5 jaar leeft nog 43% van de patiënten die behandeld zijn met ipilimumab en nivolumab, meer dan 10% bereikt een complete response en na 5 jaar is 31% zonder progressie (Bedke, 2021). Dit betekent dat twee groepen patiënten baat kunnen hebben bij een cytoreductieve nefrectomie na immuuntherapie:

1. Patiënten met een complete of bijna complete response van de afstandsmetastasen die na een aanvullende cytoreductieve nefrectomie ziektevrij (no evidence of disease, (NED)) zijn en daardoor mogelijk met therapie kunnen stoppen
2. Patiënten met een partiële response of stabiele ziekte van de metastasen (e.g. controle van de afstandsmetastasering) bij wie de primaire tumor ondanks immuuntherapie toeneemt in omvang

Tegenwoordig kunnen 4 redenen worden geïdentificeerd ter ondersteuning van het bovengenoemde beleid:

1. Een *pathologische* complete response in de primaire tumor na immuuntherapie is beschreven maar zeldzaam. Een cytoreductieve nefrectomie bij patiënten met complete response van de afstandsmetastasen kan daarom bijdragen tot een daadwerkelijke ziektevrije situatie.
2. Dit word verder ondersteund door translationeel onderzoek in de TRACERx studie (Turajlic, 2018; Turaljic_1, 2018) waarin wordt aangetoond dat bij longitudinaal onderzoek patiënten in de primaire tumor ondanks eerdere respons van de metastasen een nieuwe progressieve kloon kunnen ontwikkelen. Een cytoreductieve nefrectomie kan deze ontwikkeling onderbreken of voorkomen bij patiënten met een complete of bijna complete respons van de afstandsmetastasen.
3. Ziektevrije patiënten kunnen mogelijk met maintenance therapie (nivolumab of TKI) stoppen en bijwerkingen voorkomen en kosten besparen
4. Histopathologische analyse van de primaire tumor is tegenwoordig de enige mogelijkheid om bij patiënten met een complete response van de afstandsmetastasering een complete pathologische response te bevestigen.

Het tijdstip van cytoreductieve nefrectomie is onvoldoende onderzocht, maar totdat bewijs uit gerandomiseerde studies beschikbaar komt, strekt het tot aanbeveling om duurzame respons aan te tonen. In de meeste immuuntherapie studies was de mediane tijd tot best respons 4.5 maanden (Bedke, 2018). Twee aansluitende interval beoordelingen met beeldvorming om aanhoudende response te documenteren worden als redelijk beschouwd alvorens tot cytoreductieve nefrectomie te besluiten. Daarbij wordt verondersteld dat de omvang van de primaire tumor niet toeneemt. Dit betekent in de praktijk dat bij patiënten na bereiken van een complete of bijna complete response van de afstandsmetastasen na 10-12
maanden na start immuuntherapie een cytoreductieve nefrectomie kan worden overwogen. Dit komt overeen in retrospectieve studies met de gerapporteerde mediane tijd tot cytoreductieve nefrectomie na immuuntherapie met nivolumab en ipilimumab (13,8 maanden, Meerveld-Eggink, 2022).

In retrospectieve series werd moeizame dissectie (verklevingen, inflammatie) beschreven tijdens de cytoreductieve nefrectomie na immuuntherapie en een hoge kans op postoperatieve complicaties (Graafland, 2022; Pignot, 2019). De mate van bewijs is laag omdat de studies niet vergelijkend zijn en de tumoren een a priori grote kans op complicatie hebben door hun omvang en slechte performance status van de meeste patiënten.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
De waarden en voorkeuren van patiënten zijn onvoldoende onderzocht en beschreven maar het is aannemelijk dat patiënten de kans op een ziektevrije situatie als positief beschouwen. Voor patiënten met bijwerkingen van de maintenance immuuntherapie of TKI kan een onderbreking van de therapie in een ziektevrije periode een groot voordeel betekenen.
Het is van belang patiënten goed over het beoogde doel en de mate van bewijs van de cytoreductieve nefrectomie na immuuntherapie te informeren om tot een weloverwogen keuze te komen. Zo moet worden besproken dat bewijs uit gerandomiseerde studies ontbreekt of de operatie tot verlenging van overleving kan leiden. Het primaire doel is een ziektevrije situatie te bereiken bij patiënten met een complete of bijna complete response van de afstandsmetastasen. De lengte van deze ziektevrije periode is onbekend maar kan in individuele gevallen van lange duur zijn en mogelijk zelfs gelijk staan aan genezing. Dit biedt de mogelijkheid onderhoudstherapie langdurig te stoppen, maar het is onvoldoende onderzocht of stoppen van de behandeling in deze situaties ook veilig is.
De situatie is anders voor patiënten bij wie de primaire tumor groeit ondanks controle van de afstandsmetastasen door immuuntherapie. Hier is het beoogde doel om lokale problemen door de tumorgroei te voorkomen. Een lokale therapie (cytoreductive therapie) heeft dan de voorkeur boven verandering naar tweede of een volgende lijn systeemtherapie.

Kosten (middelenbeslag)
Onderhoudstherapie met nivolumab of TKI is duur en een ziektevrije en therapie-vrije periode kan een individueel en maatschappelijk gunstig financieel gevolg hebben. Er is geen budget-impact analyse uitgevoerd of het uitvoeren van een cytoreductieve nefrectomie en/of embolisatie meer kosteneffectief is. Het therapie-vrije interval met deze aanpak is nu ongeveer 2.5 jaar (Fransen van de Putten, 2022).

Aanvaardbaarheid, haalbaarheid en implementatie
De meeste regionale ziekenhuizen zijn bekwaam in het uitvoeren van een cytoreductieve nefrectomie. De indicaties voor cytoreductieve nefrectomie zijn minder geworden in vergelijking met voorafgaande jaren wat betekent dat er voldoende capaciteit zou moeten zijn voor de zeer beperkte getallen. Retrospectieve series laten zien dat tussen de 18-20% van patiënten met een primair gemetastaseerd niercelcarcinoom behandeld met immuuntherapie in aanmerking komt voor een cytoreductieve nefrectomie gebaseerd op bovengenoemde indicaties (Meerveld Eggink, 2022; Fransen van de Putten, 2023).

Aanbevelingen
Aanbeveling-1
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Patiënten met een complete of bijna complete response van de metastasen kunnen baat hebben bij een aanvullende cytoreductieve nefrectomie om ziektevrije situatie (no evidence of disease (NED)) te bereiken en mogelijk met therapie te kunnen stoppen. Ondersteunende argumenten zijn:

1. Een pathologische complete response in de primaire tumor na immuuntherapie is beschreven maar zeldzaam. Een cytoreductieve nefrectomie bij patiënten met

complete respons van de afstandsmetastasen kan daarom bijdragen tot een daadwerkelijke ziektevrije situatie.
2. Dit word verder ondersteund door translationeel onderzoek in de TRACERx studie (Turajlic, 2018) waarin kon worden aangetoond dat bij longitudinaal onderzoek patiënten in de primaire tumor ondanks eerdere respons van de metastasen een nieuwe progressieve kloon kunnen ontwikkelen. Een cytoreductieve nefrectomie kan deze ontwikkeling onderbreken of voorkomen bij patiënten met een complete of bijna complete respons van de afstandsmetastasen.
3. Ziektevrije patiënten kunnen mogelijk met maintenance therapie (nivolumab of TKI) stoppen wat bijwerkingen voorkomt en kosten bespaart
4. Histopathologische analyse van de primaire tumor is tegenwoordig de enige mogelijkheid om bij patiënten met een complete response van de afstandsmetastasering een complete pathologische response te bevestigen.
5. Data van gerandomiseerde studies zullen pas over een aantal jaren beschikbaar zijn. In de tussentijd is er behoefte aan een praktijkgerichte aanbeveling

De mate van bewijs is echter laag en moet met de patiënt worden besproken (zwakke aanbeveling).

Het tijdstip van cytoreductieve nefrectomie bij patiënten met een complete of bijna complete respons van de afstandsmetastasen is onvoldoende onderzocht maar tot verder bewijs uit gerandomiseerde studies beschikbaar komt strekt het tot aanbeveling om duurzame respons aan te tonen. In de meeste immuuntherapie studies was de mediane tijd tot best response 4.5 maanden (Choueiri, 2024; Motzer, 2023; Motzer, 2024). Twee aansluitende interval beoordelingen met beeldvorming ter documentatie van aanhoudende respons zijn nodig alvorens tot cytoreductieve nefrectomie te besluiten, verondersteld dat de omvang van de primaire tumor niet toeneemt. Dit betekent in de praktijk dat bij patiënten na bereiken van een complete of bijna complete response van de afstandsmetastasen na 10-12 maanden na start van immuuntherapie een cytoreductieve nefrectomie kan worden overwogen. Dit komt ook overeen met de gerapporteerde mediane tijd tot cytoreductieve nefrectomie in retrospectieve studies na immuuntherapie met nivolumab en ipilimumab (13.8 maanden, Meerveld-Eggink ref).

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.

<u>Aanbeveling-subgroep patiënten met response van metastasen en groei primaire tumor</u>
<u>Rationale van de aanbeveling: weging van de argumenten voor en tegen de interventie voor patiënten met response van metastasen en groei primaire tumor</u>
Patiënten met controle van afstandsmetastasen kunnen nadelen ondervinden door groei van de lokale tumor. Hierdoor kan een lokaal bedreigende situatie ontstaan ondanks een algemene ziekte controle of stabilisatie. Deze situatie is echter zeldzaam maar beschreven bij patiënten met immuuntherapie (Fransen van de Putte, 2023). De lokale behandeling (cytoreductieve nefrectomie) kan progressie onderbreken en de noodzaak tot verandering van systeemtherapie afwenden.

Overweeg een cytoreductieve nefrectomie na immuuntherapie bij patiënten bij wie de primaire tumor groeit ondanks controle van de afstandsmetastasen.

Kennislacunes

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

Literatuur

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Module 6 Adjuvante behandeling

Uitgangsvraag
Wat is de plaats van adjuvante therapie in de behandeling van patiënten met niercelcarcinoom zonder aanwijzing voor ziekte na operatie?

Inleiding
Van meerdere studies met immuuntherapie heeft slechts een studie met adjuvant pembrolizumab een verbetering van DFS en OS laten zien en is inmiddels door de EMA geregistreerd. In het TKI-tijdperk heeft van meerdere studies alleen een studie met sunitinib een verbetering van DFS getoond maar werd niet door de EMA geregistreerd.

Search and select
A systematic review of the literature was performed to answer the following question:
What are the (un)desirable effects of adjuvant therapy compared to no adjuvant therapy in patients with non-metastatic renal cell carcinoma?

P: patients with renal cell carcinoma after surgery with no evidence of disease
I: adjuvant therapy (sunitinib, cabozantinib, pazopanib, pembrolizumab, avelumab, ipilimumab, nivolumab)
C: no adjuvant therapy (placebo or observation)
O: disease-free survival, overall survival, quality of life, adverse events (toxicity)

<u>Relevant outcome measures</u>
The guideline development group considered survival and progression-free survival a critical outcome measure for decision making; and quality of life as an important outcome measure for decision making.

The working group followed the definitions of the outcome measures as described in the included literature.

The working group used the GRADE default boundaries for clinical relevance (0.80-1.25) for all outcome measures as minimal clinically (patient) important differences.

<u>Search and select (Methods)</u>
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 25-04-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 37 hits. Studies were selected based on the following criteria: systematic reviews, RCT's and observational studies. Studies were initially selected based on title and abstract screening. After reading the full text, 36 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 1 study was included. The search was updated on the 22nd of December 2023. The updated literature search yielded another 529 hits. After reading the full text, out of 14 studies a total of 10 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 4 additional studies were included in the literature analysis.
Thus the literature analysis contains 5 studies in total.

Results

5 of studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Adjuvant Tyrosine kinase inhibitors versus placebo

Description of studies

Riaz, 2021 performed a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating risk-benefit for adjuvant postoperative treatments in high-risk renal cell carcinoma by assessing reported disease-free survival (DFS), overall survival (OS), toxicity, and quality of life. A literature search was performed in PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials to identify relevant RCTs (from database inception through May 15, 2018). The results of the ATLAS trial were published while writing this manuscript, and the manuscript was updated accordingly. Four phase 3 clinical trials with a total of 4820 patients were included in qualitative analysis and meta-analysis.

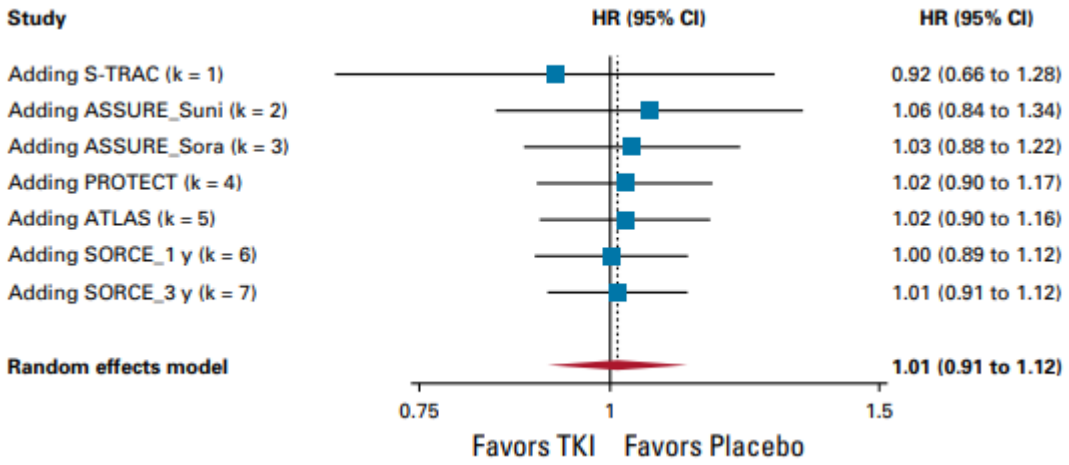
Results

Both disease free survival (DFS) and overall survival (OS) did not benefit from adjuvant tyrosine kinase inhibitors (TKIs). The highest-risk patients demonstrated no benefit in DFS in the subgroup analysis of either risk category. However the definition of highest risk varied across trials.

Therapy with TKI resulted in a higher risk of all-cause adverse event (AE) of any grade and all-cause adverse event (AE) of grade ≥3 compared to the placebo.

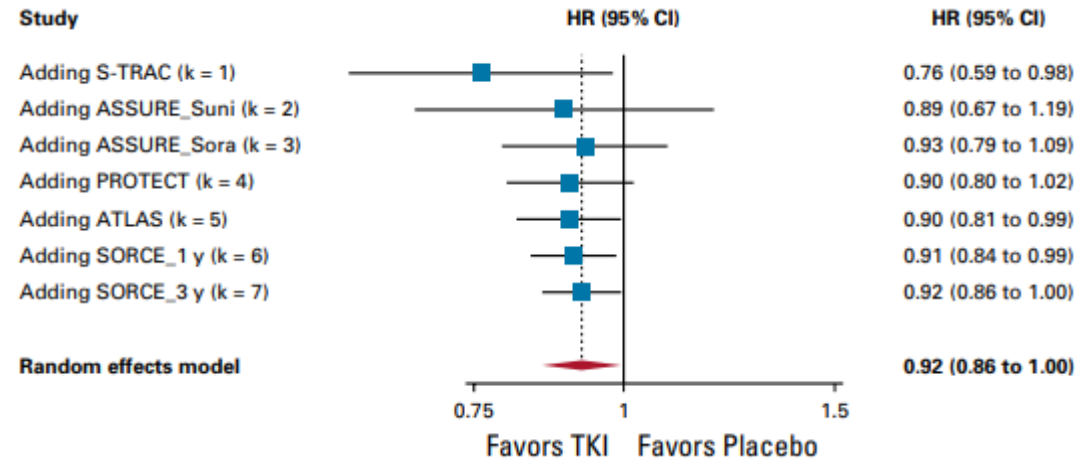
1. Overall survival

TKI monotherapy offers no benefit in Overall survival (OS) (hazard ratio, 1.01; 95% CI, 0.91 to 1.12, high certainty) and is not considered clinically relevant.



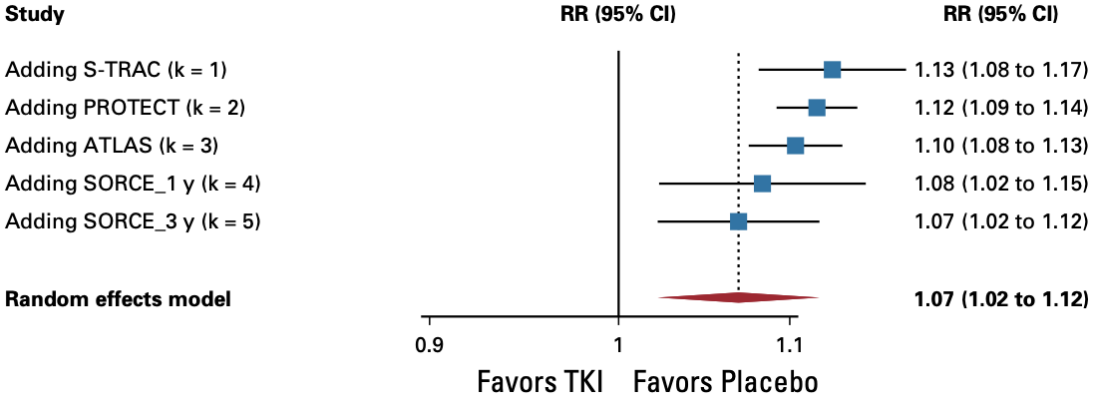
2. Disease-free survival

TKI monotherapy offers benefit in disease-free survival (DFS) (hazard ratio, 0.92; 95% CI, 0.86 to 1.00, high certainty) but this difference is not considered clinically relevant.



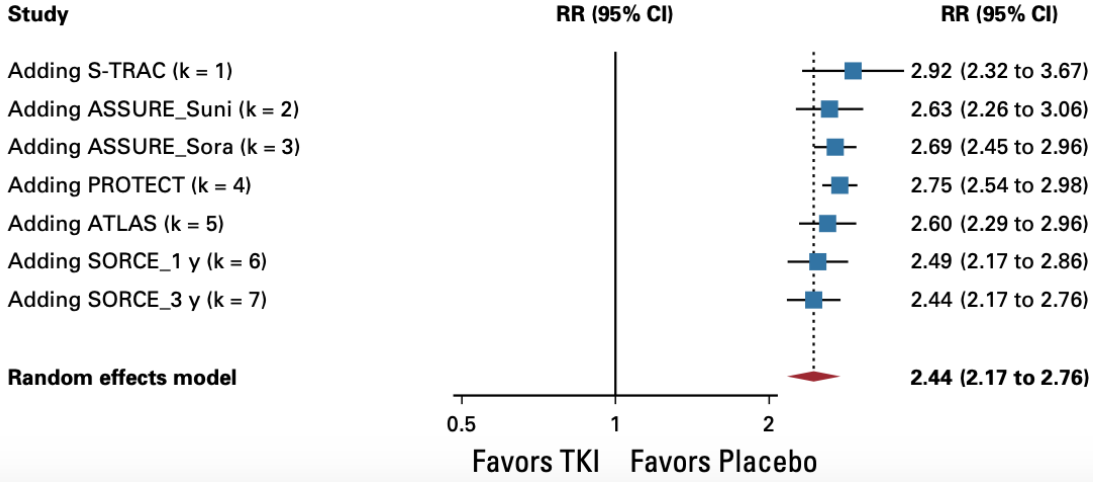
3. All-cause adverse events

TKI monotherapy offers no benefit in all-cause adverse event (AE) of any grade (hazard ratio, 1.07; 95% CI, 1.02 to 1.12, high certainty) and is not considered clinically relevant.



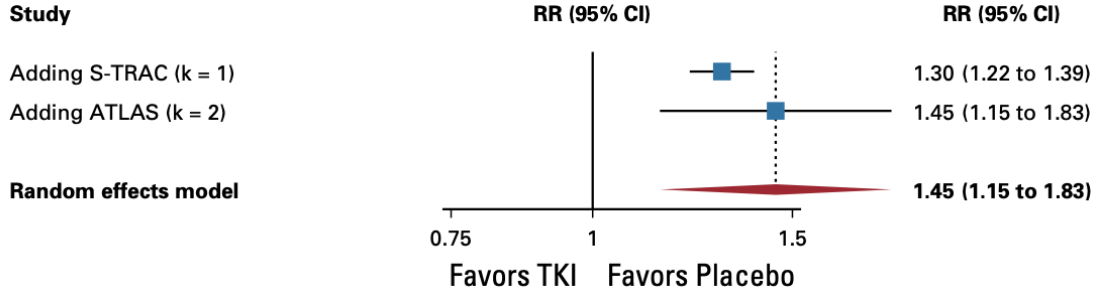
4. All-cause adverse event (AE) of grade ≥3

TKI monotherapy offers no benefit in all-cause adverse event (AE) of grade ≥3 (hazard ratio, 2.44; 95% CI, 2.17 to 2.76, high certainty) and is considered clinically relevant.



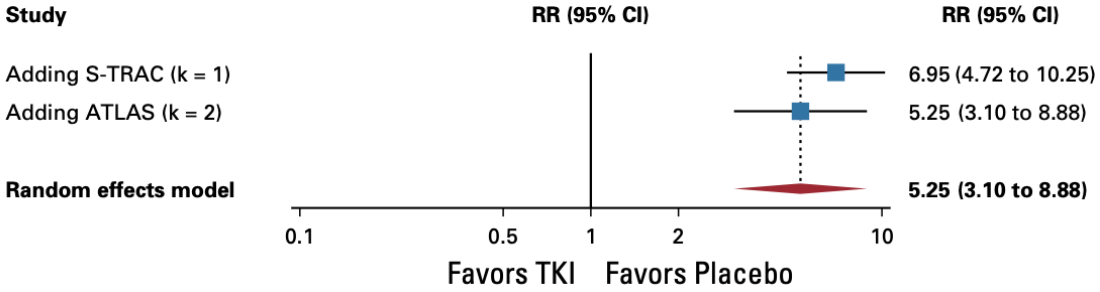
5. Treatment-related adverse events TKI monotherapy offers no benefit in treatment-related adverse events (trAEs) of any grade

(hazard ratio, 1.45; 95% CI, 1.15 to 1.83, high certainty) and is considered clinically relevant.



6. Treatment-related adverse events (trAEs) of grade ≥3treatment-related adverse events (trAEs) of grade ≥3 TKI monotherapy offers no benefit in treatment-related adverse events (trAEs) of grade ≥3

(hazard ratio, 5.25; 95% CI, 3.10 to 8.88, high certainty) and is considered clinically relevant.



7. Quality of life

The PROTECT, S-TRAC, and ASSURE trials included some measure of QoL as a study outcome. The PROTECT trial used the Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (FKSI-19) questionnaire to assess QoL, and although significantly greater deterioration in QoL from baseline was seen in the TKI group compared with placebo (adjusted mean change in total FKSI-19 score at 1 year: −4.49 v −0.47, P , .01), this was not considered clinically relevant and QoL scores in both groups returned to baseline after treatment cessation. Similarly, in S-TRAC, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) scores favored placebo, but the difference was not clinically meaningful. The ASSURE trial collected patient-reported data on a quality-of-life (QoL) assessment for fatigue, called PROMIS Fatigue-SF1, but these results are yet to be published.

Level of evidence of the literature

Overall survival (OS)

The level of evidence regarding the outcome measure Overall Survival started at high (RCT) and was not downgraded.

Disease-free survival (DFS)

The level of evidence regarding the outcome measure Disease-free survival started at high (RCT) and was not downgraded.

All-cause adverse event (AE) of any grade

The level of evidence regarding the outcome measure all-cause adverse event (AE) of any grade started at high (RCT) and was not downgraded.

All-cause adverse event (AE) of grade ≥3
The level of evidence regarding the outcome measure all-cause adverse event (AE) of grade ≥3 started at high (RCT) and was not downgraded.

Treatment-related adverse events (trAEs) of any grade
The level of evidence regarding the outcome measure Treatment-related adverse events (trAEs) of any grade started at high (RCT) and was downgraded by 1 level to moderate because of number of included patients (imprecision, overlap of boundary of clinical relevance).

Treatment-related adverse events (trAEs) of grade ≥3
The level of evidence regarding the outcome measure treatment-related adverse events (trAEs) of grade ≥3 started at high (RCT) and was not downgraded.

Quality of life
The level of evidence regarding the outcome measure quality of life started at high (RCT) and was downgraded by 1 level to moderate because of applicability (bias due to indirectness: different measurement tools are used thus pooling of results is not possible).

Conclusions
Overall survival

High GRADE	Adjuvant therapy with VEGFR-TKI results in little to no difference in overall survival when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Riaz, 2021*

Disease-free survival

High GRADE	Adjuvant therapy with VEGFR-TKI results in little to no difference in disease-free survival when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Riaz, 2021*

All-cause adverse event (AE) of any grade

High GRADE	Adjuvant therapy with VEGFR-TKI results in little to no difference in all-cause adverse event (AE) of any grade when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Riaz, 2021*

All-cause adverse event (AE) of grade ≥3

High GRADE	Adjuvant therapy with VEGFR-TKI increases the risk of all-cause adverse event (AE) of grade ≥3 when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma.

	Source: Riaz, 2021

Treatment-related adverse events (trAEs) of any grade

Moderate GRADE	Adjuvant therapy with VEGFR-TKI likely increases risk of treatment-related adverse events (trAEs) of any grade when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Riaz, 2021*

Treatment-related adverse events (trAEs) of grade ≥3

High GRADE	Adjuvant therapy with VEGFR-TKI increases the risk of treatment-related adverse events (trAEs) of grade ≥3 of grade ≥3 when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Riaz, 2021*

Quality of life

Moderate GRADE	Adjuvant therapy with VEGFR-TKI likely results in little to no difference in quality of life when compared with no (neo)adjuvant in patients with non-metastatic renal cell carcinoma. *Source: Riaz, 2021*

Nivolumab with or without + ipilimumab versus placebo

Description of studies

Motzer, 2013 reported **a** double-blind, randomised, trial (CheckMate 914). Patients with localised clear cell renal cell carcinoma who were at high risk of relapse after radical or partial nephrectomy between 4–12 weeks before random assignment were included.Patients were randomly assigned (1:1) to nivolumab (240 mg) intravenously every 2 weeks for 12 doses plus ipilimumab (1 mg/kg) intravenously every 6 weeks for four doses, or matching placebo, via an interactive response technology system. The expected treatment period was 2
w
eks, and treatment could be continued until week 36, allowing for treatment delays. 816 patients were randomly assigned to receive either adjuvant nivolumab plus ipilimumab (405 patients) or placebo (411 patients). 580 (71%) of 816 patients were male and 236 (29%) patients were female.

Results

1. Overall survival

The number of events required for the planned overall survival interim analysis was not reached at the time of the data cutoff, and only 61 events occurred (33 in the nivolumab plus ipilimumab group and 28 in the placebo group).

2. Disease-free survival

With a median follow-up of 37·0 months (IQR 31·3–43·7), median disease-free survival was not reached in the nivolumab plus ipilimumab group and was 50·7 months (95% CI 48·1 to not estimable) in the placebo group (hazard ratio 0·92, 95% CI 0·71–1·19; p=0·53).

3. All-cause adverse events

In the all-treated population, 392 (97%) of 404 patients who received nivolumab plus ipilimumab and 361 (89%) of 407 patients who received placebo had at least one adverse event of any grade and of any cause. All-cause adverse events of any grade led to discontinuation of nivolumab plus ipilimumab in 129 (32%) of 404 treated patients and of placebo in nine (2%) of 407 treated patients. Four deaths were attributed to treatment with nivolumab plus ipilimumab and no deaths were attributed to treatment with placebo.

4. All-cause adverse event (AE) of grade ≥3

In total, 154 (38%) of 404 patients who received nivolumab plus ipilimumab and 42 (10%) of 407 patients who received placebo had an adverse event of grade 3–5. The most common adverse events of any cause in the two arms were pruritus (32% with nivolumab plus ipilimumab and 17% with placebo), fatigue (30% with nivolumab plus ipilimumab and 27% with placebo), and diarrhoea (27% with nivolumab plus ipilimumab and 21% with placebo).

5. Treatment related adverse events

A total of 359 (89%) of 404 patients treated with nivolumab plus ipilimumab and 231 (57%) of 407 patients treated with placebo had at least one treatment-related adverse event of any grade. Treatment-related adverse events of any grade led to the discontinuation of nivolumab plus ipilimumab in 117 (29%) of 404 treated patients and of placebo in four (1%) of 407 treated patients

6. Treatment-related adverse events (trAEs) of grade ≥3treatment-related adverse events (trAEs) of grade ≥3

28% of patients treated with nivolumab plus ipilimumab experienced a treatment-related adverse event of grade 3 or 4 as compared to 2% of patients treated with placebo.

7. Quality of life

Not reported.

Level of evidence of the literature

Overall survival (OS)

The level of evidence regarding the outcome measure Overall Survival started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

Disease-free survival (DFS)

The level of evidence regarding the outcome measure Disease-free survival started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

All-cause adverse event (AE) of any grade

The level of evidence regarding the outcome measure all-cause adverse event (AE) of any grade started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

All-cause adverse event (AE) of grade ≥3

The level of evidence regarding the outcome measure all-cause adverse event (AE) of grade ≥3 started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

Treatment-related adverse events (trAEs) of any grade
The level of evidence regarding the outcome measure Treatment-related adverse events (trAEs) of any grade started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

Treatment-related adverse events (trAEs) of grade ≥3
The level of evidence regarding the outcome measure treatment-related adverse events (trAEs) of grade ≥3 started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

Quality of life
This outcome was not reported and could not be graded.

Conclusions

Overall survival

Low GRADE	Nivolumab with or without ipilimumab therapy may result in little to no difference in overall survival when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Motzer, 2023*

Disease-free survival

Low GRADE	Nivolumab with or without ipilimumab therapy may result in little to no difference in disease-free survival when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Motzer, 2023*

All-cause adverse event (AE) of any grade

Low GRADE	Nivolumab plus ipilimumab therapy may increase the risk of all-cause adverse event (AE) of any grade when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Motzer, 2023*

All-cause adverse event (AE) of grade ≥3

Low GRADE	Nivolumab plus ipilimumab therapy may increase the risk of all-cause adverse event (AE) of grade ≥3 when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Motzer, 2023*

Treatment-related adverse events (trAEs) of any grade

Low GRADE	Nivolumab plus ipilumanb therapy may increase the risk of treatment-related adverse events (trAEs) of any grade when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Motzer, 2023*

Treatment-related adverse events (trAEs) of grade ≥3

Low GRADE	Nivolumab plus ipilumanb therapy may increase the risk of treatment-related adverse events (trAEs) of grade ≥3 when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: Motzer, 2023*

Quality of life

No GRADE	No evidence was found on nivolumab plus ipilumab regarding the quality of life when compared with no (neo)adjuvant therapy in patients with non-metastatic renal cell carcinoma. *Source: -*

Pembrolizumab versus placebo

Description of studies

A total of three publications, describing one study reported **a** double-blind, randomised, trial (Keynote 564): Choueiri, 2021; Choueiri, 2024 and Powles 2022. A fourth publication updating overall survival was published after the literature search and shall be discussed in "Overwegingen – van bewijs tot aanbeveling" at the end of this chapter to support the recommendation. Patients with localised clear cell renal cell carcinoma with an increased risk of recurrence were included. Eligible participants had an Eastern Cooperative Oncology Group performance status of 0 or 1, had undergone nephrectomy 12 weeks or less before randomisation, and had not received previous systemic therapy for advanced renal cell carcinoma. The risk of disease recurrence was classified according to protocol-defined criteria as intermediate to high (tumor stage T2 with nuclear grade 4 or sarcomatoid features, or tumor stage T3; no regional lymph node or distant metas tasis present), high (tumor stage T4 with no regional lymph node or distant metastasis, or any tumor stage with the presence of regional lymph-node involvement), or stage M1 NED (no evidence of disease). Patients were randomly assigned to pembrolizumab 200 mg (n=496) or placebo (n=498) 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. Dose modifications for pembrolizumab were not permitted. Some patients had metastases and randomisation was stratified by metastatic disease status (M0 vs M1), and the M0 group was further stratified by ECOG performance status and geographical region.
Choueiri, 2021 reported the outcomes at the median time from randomization to the data-cutoff date of 24.1 months.

Powles reported long-term follow-up outcomes. The median follow-up (time from randomisation to the data cutoff date of June 14, 2021) was 30·1 months (IQR 25·7–36·7). The median number of treatment cycles administered was 17 (IQR 9–17) in the pembrolizumab group and 17 (16–17) in the placebo group. Among participants who received at least one dose of study treatment, 298 (61%) of 488 in the pembrolizumab group and 366 (74%) of 496 in the placebo group completed all 17 planned cycles of treatment.
Choueiri, 2024 reported the health-related quality of life (HRQoL) compared between treatment and placebo group. This was assessed by the European Organization for Research and Treatment of Cancer core quality of life questionnaire, (EORTC QLQ-C3)0 global health status/quality of life (GHS/QoL) and physical functioning scale scores and Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index—Disease-Related Symptoms (FKSI-DRS).

Results

1. Overall survival
Chioueri, 2021 reports a total of 51 deaths (18 in the pembrolizumab group and 33 in the placebo group). The median overall survival was not reached in either group (hazard ratio for death, 0.54; 95% CI, 0.30 to 0.96).
Powles, 2022 reports similar results: overall survival was better with pembrolizumab compared with placebo (HR 0.52 (95% CI 0.31–0.86). At 30 months follow up also median overall survival was not reached in either group. At 30 months, the estimated proportion of participants who were alive was 95.7% (95% CI 93.3–97.2) in the pembrolizumab group and 91.4% (88.3–93.7) in the placebo group.

2. Disease-free survival
Chioueri, 2021 reports that as of the data-cutoff date, 260 events of disease recurrence or death had occurred (109 events in the pembrolizumab group and 151 in the placebo group). The median disease-free survival was not reached in either group. The risk of disease recurrence or death was 32% lower with adjuvant pembrolizumab therapy than with placebo (hazard ratio for recurrence or death, 0.68; 95% confidence interval [CI], 0.53 to 0.87; P=0.002 [two-sided]).
Powles, 2022 reports similar results: disease-free survival was better with pembrolizumab compared with placebo (HR 0·63 [95% CI 0·50–0·80]) in the intention-to-treat population. Median disease-free survival was not reached in either group.

3. All-cause adverse events
Chioueri, 2021 reports that in the as-treated population, 96.3% of the patients who received pembrolizumab and 91.1% of those who received placebo had at least one adverse event of any grade and of any cause.
Powles, 2021 reports that the adverse event profile of pembrolizumab was in line with those reported for this study previously, with no new safety signals.

4. All-cause adverse event (AE) of grade ≥ 3
Chioueri, 2021, describes that in total, 32.4% of the patients who received pembrolizumab and 17.7% of those who received placebo had an adverse event of grade 3 to 5. There were two deaths in the pembrolizumab group, which were due to multiple organ dysfunction syndrome and pneumonia (in one patient each), and one death in the

placebo group, which was due to intracranial hemorrhage,Powles, 2021 states that Grade 3 or worse adverse events of any cause were reported in 157 (32%) of 488 participants in the pembrolizumab group and 88 (18%) of 496 participants in the placebo group. The most common grade 3 or worse adverse events of any cause were hypertension (in 14 [3%] participants) and increased alanine aminotransferase (11 [2%] participants) in the pembrolizumab group and hypertension (13 [3%] participants) in the placebo group.

5. Treatment related adverse events

Chioueri repoerted that a total of 386 patients (79.1%) who received pembrolizumab and 265 (53.4%) who received placebo had at least one adverse event of any grade that was attributed to pembrolizumab or placebo by the investigator, including an event of grade 3 or 4 in 18.9% of the patients who received pembrolizumab and 1.2% of those who received placebo.
Powles, 2022 did not report treatment related adverse events specifically.

6. Treatment-related adverse events (trAEs) of grade ≥3treatment-related adverse events (trAEs) of grade ≥3

Chioueri, 2021 describes that no deaths that were attributed to either pembrolizumab or placebo occurred. At least one treatment-related serious adverse event occurred in 12.1% of the patients who received pembrolizumab and in 0.2% of those who received placebo.
Powles, 2022 similarly states that no deaths from treatment-related adverse events occurred in either study group. Serious adverse events attributed to study treatment occurred in 59 (12%) participants in the pembrolizumab group and one (<1%) participant in the placebo group. The most common serious treatment-related adverse events (≥1% incidence) in the pembrolizumab group were adrenal insufficiency (six [1%] participants), colitis (six [1%]), and diabetic ketoacidosis (five [1%])

7. Quality of life

Chioueri, 2024 reported that adjuvant treatment with pembrolizumab did not result in deterioration of HRQoL. No clinically meaningful difference in least squares mean scores for pembrolizumab versus placebo were observed at week 52 for EORTC QLQ-C30 GHS/QoL (–2.5; 95% CI –5.2 to 0.1), EORTC QLQ-C30 physical functioning (–0.87; 95% CI –2.7 to 1.0), and FKSI-DRS (–0.7; 95% CI –1.2 to –0.1). Most PRO scores remained stable or improved for the EORTC QLQ-C30 GHS/QoL (pembrolizumab, 54.3%; placebo, 67.5%), EORTC QLQ-C30 physical functioning (pembrolizumab, 64.7%; placebo, 68.8%), and FKSI-DRS (pembrolizumab, 58.2%; placebo, 66.3%).

Level of evidence of the literature

Overall survival (OS)

The level of evidence regarding the outcome measure Overall Survival started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers, confidence interval crossing border for clinical relevance).

Disease-free survival (DFS)

The level of evidence regarding the outcome measure Disease-free survival started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers, confidence interval crossing border for clinical relevance).

All-cause adverse event (AE) of any grade
The level of evidence regarding the outcome measure all-cause adverse event (AE) of any grade started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers) and heterogeneity.

All-cause adverse event (AE) of grade ≥3
The level of evidence regarding the outcome measure all-cause adverse event (AE) of grade ≥3 started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

Treatment-related adverse events (trAEs) of any grade
The level of evidence regarding the outcome measure Treatment-related adverse events (trAEs) of any grade started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers) and heterogeneity.

Treatment-related adverse events (trAEs) of grade ≥3
The level of evidence regarding the outcome measure treatment-related adverse events (trAEs) of grade ≥3 started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers) and heterogeneity.

Quality of life
The level of evidence regarding the outcome measure Overall Survival started at high (RCT) and was downgraded by two levels to low due to imprecision (wide confidence intervals).

Conclusions
Overall survival

Low GRADE	Adjuvant pembrolizumab therapy may result in a better overall survival when compared with placebo in patients with renal cell carcinoma and the following risk profile: • intermediate to high (tumor stage T2 with nuclear grade 4 or sarcomatoid features, or tumor stage T3; no regional lymph node or distant metastasis present), • high (tumor stage T4 with no regional lymph node or distant metastasis, or any tumor stage with the presence of regional lymph-node involvement), or • stage M1 NED (resected to no evidence of disease). *Source: Chioueri, 2021; Powles, 2022*

Disease-free survival

Low GRADE	Adjuvant pembrolizumab therapy may result in a better in disease-free survival when compared with placebo in patients with renal cell carcinoma and the following risk profile: • intermediate to high (tumor stage T2 with nuclear grade 4 or sarcomatoid features, or tumor stage T3; no regional lymph node or distant metastasis present),

	• high (tumor stage T4 with no regional lymph node or distant metastasis, or any tumor stage with the presence of regional lymph-node involvement), or • stage M1 NED (resected to no evidence of disease). *Source: Chioueri, 2021; Powles, 2022*

All-cause adverse event (AE) of any grade

Low GRADE	Adjuvant pembrolizumab therapy may result in little to no difference in the risk of all-cause adverse event (AE) of any grade when compared with placebo in patients with renal cell carcinoma and the following risk profile: • intermediate to high (tumor stage T2 with nuclear grade 4 or sarcomatoid features, or tumor stage T3; no regional lymph node or distant metastasis present), • high (tumor stage T4 with no regional lymph node or distant metastasis, or any tumor stage with the presence of regional lymph-node involvement), or • stage M1 NED (resecterd to no evidence of disease). *Source: Chioueri, 2021; Powles, 2022*

All-cause adverse event (AE) of grade ≥3

Low GRADE	Adjuvant pembrolizumab therapy may increase the risk of all-cause adverse event (AE) of grade ≥3 when compared with placebo in patients with renal cell carcinoma and the following risk profile: • intermediate to high (tumor stage T2 with nuclear grade 4 or sarcomatoid features, or tumor stage T3; no regional lymph node or distant metastasis present), • high (tumor stage T4 with no regional lymph node or distant metastasis, or any tumor stage with the presence of regional lymph-node involvement), or • stage M1 NED (resected to no evidence of disease). *Source: Chioueri, 2021; Powles, 2022*

Treatment-related adverse events (trAEs) of any grade

Low GRADE	Adjuvant pembrolizumab therapy may increase the risk of treatment-related adverse events (trAEs) of any grade when compared with placebo in patients with renal cell carcinoma and the following risk profile: • intermediate to high (tumor stage T2 with nuclear grade 4 or sarcomatoid features, or tumor stage T3; no regional lymph node or distant metastasis present), • high (tumor stage T4 with no regional lymph node or distant metastasis, or any tumor stage with the presence of regional lymph-node involvement), or • stage M1 NED (resected to no evidence of disease). *Source: Chioueri, 2021; Powles, 2022*

Treatment-related adverse events (trAEs) of grade ≥3

Low GRADE	Adjuvant pembrolizumab therapy may increase the risk of treatment-related adverse events (trAEs) of grade ≥3 when compared with placebo in patients with renal cell carcinoma and the following risk profile: • intermediate to high (tumor stage T2 with nuclear grade 4 or sarcomatoid features, or tumor stage T3; no regional lymph node or distant metastasis present), • high (tumor stage T4 with no regional lymph node or distant metastasis, or any tumor stage with the presence of regional lymph-node involvement), or • stage M1 NED (resected to no evidence of disease). *Source: Chioueri, 2021; Powles, 2022*

Quality of life

Low GRADE	Adjuvant pembrolizumab therapy may result in little to no difference in health-related quality of life when compared with placebo in patients with renal cell carcinoma and the following risk profile: • intermediate to high (tumor stage T2 with nuclear grade 4 or sarcomatoid features, or tumor stage T3; no regional lymph node or distant metastasis present), • high (tumor stage T4 with no regional lymph node or distant metastasis, or any tumor stage with the presence of regional lymph-node involvement), or • stage M1 NED (resected to no evidence of disease). *Source: Chioueri, 2024*

Atezolizumab versus placebo

Description of studies

Pal, 2022 reported **a** double-blind, randomised, trial (IMmotion010). Eligible patients were patients aged 18 years or older with renal cell carcinoma with a clear cell or sarcomatoid component and increased risk of recurrence. After nephrectomy with or without metastasectomy, patients were randomly assigned (1:1) to receive atezolizumab (1200 mg) or placebo (both intravenous) once every 3 weeks for 16 cycles or 1 year. Patients with metastases were eligible for inclusion. Stratification factors were disease stage (T2 or T3a vs T3b–c or T4 or N+ vs M1 no evidence of disease), geographical region (north America [excluding Mexico] vs rest of the world), and PD-L1 status on tumour-infiltrating immune cells. 778 patients were enrolled; 390 (50%) were assigned to the atezolizumab group and 388 (50%) to the placebo group. The median follow-up duration was 44.7 months (IQR 39·1–51·0).

Results

1. Overall survival

At data cutoff, the overall survival was immature and patients alive were censored. There were 107 deaths, 54 (14%) in the atezolizumab group and 53 (14%) in the placebo group. There was no evidence of a reduced risk of death from any cause with

adjuvant atezolizumab compared with placebo (HR 0.97, 95% CI 0.67–1.42). The 3-year overall survival rate was 90.3% (95% CI 87.3–93.3) in the atezolizumab group and 89.8% (86.6–92.9) in the placebo group.

2. Disease-free survival

332 events of investigator-assessed disease-free survival occurred (164 [42%] events in the atezolizumab group and 168 [43%] in the placebo group. Median disease-free survival (investigator assessment) was 57·2 months (95% CI 44.6 to not estimable) in the atezolizumab group and 49.5 months (47.4 to not estimable) in the placebo group (HR 0.93, 95% CI 0.75–1.15; p=0·50). 3-year disease-free survival was 59.4% (95% CI 54.4–64.5) in the atezolizumab group and 59.0% (54.0–64.0) in the placebo group. The corresponding percentages at 1 year were 77.4% (73.2–81.6; atezolizumab) and 74.1% (69.7–78.5; placebo), and 67.3% (62.6–72.1; atezolizumab) and 65.0% (60.2–69.9; placebo) at 2 years.

3. All-cause adverse events

Adverse events of any grade were reported in 373 (96%) patients who received atezolizumab and 341 (89%) patients who received placebo. Adverse events that occurred in at least 15% of patients who received atezolizumab were fatigue in 109 (28%) patients, diarrhoea in 87 (22%), arthralgia in 78 (20%), and pruritus in 74 (19%), whereas those occurring in at least 15% of patients who received placebo were fatigue in 93 (24%) and diarrhoea in 79 (21%).

4. All-cause adverse event (AE) of grade ≥3

Grade 3–4 adverse events occurred in 106 (27%) patients who received atezolizumab and 81 (21%) patients who received placebo.

There were four deaths due to adverse events in the study, one among patients who received atezolizumab and three among patients who received placebo. One patient who received atezolizumab died due to acute myeloid leukaemia. Among patients who received placebo, deaths due to adverse events resulted from respiratory failure, sepsis, and unknown cause.

5. Treatment related adverse events

296 patients (76%) who received atezolizumab and 203 (53%) who received placebo experienced at least one adverse event deemed by investigators as related to atezolizumab or placebo. Adverse events related to treatment that occurred in more than 10% of patients in the atezolizumab group were fatigue in 77 (20%) patients, pruritus in 56 (14%), hypothyroidism in 52 (13%), and diarrhoea in 45 (12%); those occurring in more than 10% of patients in the placebo group were fatigue in 69 (18%) patients, pruritus in 40 (10%), and diarrhoea in 39 (10%).

6. Treatment-related adverse events (trAEs) of grade ≥3treatment-related adverse events (trAEs) of grade ≥3

Grade 3–4 adverse events related to treatment occurred in 55 (14%) patients who received atezolizumab and 18 (5%) who received placebo. The most common grade 3–4 adverse events were hypertension (seven [2%] patients who received atezolizumab versus 15 [4%] patients who received placebo), hyperglycaemia (ten [3%] vs six [2%]), and diarrhoea (two [1%] vs seven [2%]). There were no deaths attributed to treatment.

7. Quality of life
Not reported.

Level of evidence of the literature
Overall survival (OS)
The level of evidence regarding the outcome measure Overall Survival started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

Disease-free survival (DFS)
The level of evidence regarding the outcome measure Disease-free survival started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

All-cause adverse event (AE) of any grade
The level of evidence regarding the outcome measure all-cause adverse event (AE) of any grade started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

All-cause adverse event (AE) of grade ≥3
The level of evidence regarding the outcome measure all-cause adverse event (AE) of grade ≥3 started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

Treatment-related adverse events (trAEs) of any grade
The level of evidence regarding the outcome measure Treatment-related adverse events (trAEs) of any grade started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

Treatment-related adverse events (trAEs) of grade ≥3
The level of evidence regarding the outcome measure treatment-related adverse events (trAEs) of grade ≥3 started at high (RCT) and was downgraded by two levels to low due to imprecision (low event numbers).

Quality of life
This outcome was not reported and could not be graded.

Conclusions
Overall survival

Low GRADE	Adjuvant atezolizumab therapy may result in little to no difference in overall survival when compared with placebo in patients with renal cell carcinoma. *Source: Pal, 2022*

Disease-free survival

Low GRADE	Adjuvant atezolizumab therapy may result in little to no difference in disease-free survival when compared with placebo in patients with renal cell carcinoma. *Source: Pal, 2022*

All-cause adverse event (AE) of any grade

Low GRADE	Adjuvant atezolizumab therapy may result in little to no difference in the risk of all-cause adverse event (AE) of any grade when compared with placbo in patients with renal cell carcinoma. *Source: Pal, 2022*

All-cause adverse event (AE) of grade ≥3

Low GRADE	Adjuvant atezolizumab therapy may increase the risk of all-cause adverse events (AE) of grade ≥3 when compared with placebo in patients with renal cell carcinoma. *Source: Pal, 2022*

Treatment-related adverse events (trAEs) of any grade

Low GRADE	Adjuvant atezolizumab therapy may increase the risk of treatment-related adverse events (trAEs) of any grade when compared with placebo in patients with renal cell carcinoma. *Source: Pal, 2022*

Treatment-related adverse events (trAEs) of grade ≥3

Low GRADE	Adjuvant atezolizumab therapy may increase the risk of treatment-related adverse events (trAEs) of grade ≥3 when compared with placebo in patients with renal cell carcinoma. *Source: Pal, 2022*

Quality of life

No GRADE	No evidence was found on atezolizumab regarding the quality of life when compared with placebo in patients with renal cell carcinoma. *Source: -*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Voor de tyrosinekinase inhibitors is er een systematische review met 5 RCT's gepubliceerd die een hoge mate van bewijskracht levert. Samengevat leidt adjuvante therapie met VEGFR-TKI
niet tot een betere overall of klinisch relevant verschil in ziektevrije overleving vergeleken met geen (neo) adjuvante therapie bij patiënten met niet gemetastaseerd niercelcarcinoom. Wel hebben de patiënten die tyrosinekinase inhibitors kregen meer kans op bijwerkingen, met name ernstige bijwerkingen ≥graad 3. De kwaliteit van leven is vergelijkbaar bij patiënten die wel en geen tyrosinekinase inhibitors kregen.

Voor de immuncheckpoint inhibitoren zijn 3 studies gepubliceerd tijdens de literatuursearch. Voor atezolizumab, de tot nu toe enige PD-L1 inhibitor, is er een RCT gepubliceerd met overall een lage bewijskracht, gezien de lage patiëntaantallen. Het gebruik van atezolizumab leidt niet tot een betere overall of ziekte specifieke overleving vergeleken met geen (neo)

adjuvante therapie bij patiënten met niet gemetastaseerd niercelcarcinoom. Wel hebben de patiënten die atezolizumab kregen meer kans op bijwerkingen, met name ernstige bijwerkingen ≥graad 3. De kwaliteit van leven is niet gerapporteerd bij patiënten die wel en geen atezolizumab kregen en er kan geen vergelijking worden gemaakt.

Daarnaast is er een RCT gepubliceerd voor de combinatie nivolumab en ipilimumab, een PD-1 inhibitor met anti-CTLA4 incombinatie. Deze RCT heeft overall een lage bewijskracht, gezien de lage patiëntaantallen. Het gebruik van nivolumab en ipilimumab leidt niet tot een betere overall of ziekte specifieke overleving vergeleken met geen (neo) adjuvante therapie bij patiënten met niet gemetastaseerd niercelcarcinoom. Inmiddels is, na de zoekdatum van de literatuuranalyse, ook deel B van deze RCT gepubliceerd, waarin alleen nivolumab met placebo wordt vergeleken (Motzer, 2024). Ook het gebruik van nivolumab alleen leidt niet tot een betere overall of ziekte specifieke overleving vergeleken met geen (neo) adjuvante therapie bij patiënten met niet gemetastaseerd niercelcarcinoom (Motzer, 2024). Wel hebben de patiënten die nivolumab en ipilimumab kregen meer kans op bijwerkingen, met name ernstige bijwerkingen ≥graad 3. De kwaliteit van leven is niet gerapporteerd bij patiënten die wel en geen nivolumab en ipilimumab kregen en er kan geen vergelijking worden gemaakt.

Wat betreft pembrolizumab is de Keynote studie gepubliceerd: een RCT met overall een lage bewijskracht, gezien de lage patiëntaantallen (Chioueri, 2021; Powqles, 2022). Het gebruik van pembrolizumab kan leiden tot een betere overall overleving en ziektevrije overleving vergeleken met placebo bij patiënten met niet gemetastaseerd niercelcarcinoom in de intermediate of hoge risico groep of M1 NED (no evidence of disease). Wel hebben de patiënten die pembrolizumab krijgen mogelijk meer risico op ernstige (graad 3 of hoger) bijwerkingen, terwijl de kwaliteit van leven vergelijkbaar is met de patiënten die placebo kregen.

Na de literatuursearch datum is er een update gepubliceerd van de Keynote studie (Choueiri, april 2024), waarin de uitkomsten bij een mediane follow-up van 57.2 maanden werden gerapporteerd. Bij de langere follow-up lijkt het effect van pembrolizumab op overleving nog gunstiger te worden. Met pembrolizumab werd een significante verbetering van de overall overleving waargenomen vergeleken met placebo (hazard ratio voor overlijden, 0,62; 95% BI, 0,44 tot 0,87). De geschatte totale overleving na 48 maanden was 91,2% in de pembrolizumab-groep, vergeleken met 86,0% in de placebogroep. Het gebruik van pembrolizumab ging gepaard met een hogere incidentie van ernstige bijwerkingen (20,7%, versus 11,5% met placebo) en van graad 3 of 4 bijwerkingen gerelateerd aan pembrolizumab of placebo (18,6% vs. 1,2%).

Hieruit valt af te leiden dat de Number Needed to treat om 1 sterfgeval binnen 57 maanden te voorkomen is in dit geval 17 (95% CI: 9.5 – 53.7). Voor de ziektevrije overleving is de NNT: 11 (95% CI: 6.3 – 26).
Wat betreft het risico op bijwerkingen van graad 3 of 4 is de Number Needed to Harm: 6 (95% 4.8 – 7.3).

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
Verschillende patientenorganisaties hebben op het gevaar van overbehandeling gewezen en het gebrek aan biomarkers die kunnen bepalen wie een recidief ontwikkeld en bij wie pembrolizumab een recidief kan voorkomen en eisen verder onderzoek (Apolo, 2022). Ook bestaat bij patientenorganisaties onzekerheid over het feit dat andere studie met middelen

die effectief blijken te zijn in de gemetastaseerde situatie niet werkzaam bleken in adjuvante studies.

Kosten (middelenbeslag)
Er zijn geen kosten-effectiviteitsstudies naar de effecten van adjuvante therapie bij patiënten met niercelcarcinoom die te vertalen zijn naar de Nederlandse situatie. Pembrolizumab is nog tot 2028 in patent en de te verwachten kosten van deze behandeling zijn EUR 100 000 per patiënt indien deze volgens protocol gedurende 1 jaar word gegeven, waarbij in Nederland minimaal 400 patienten per jaar in aanmerking komen. Hier tegenover staat dat bij ruim 30% een recidief (tijdelijk) word voorkomen. Hierdoor kunnen de kosten voor de duurdere combinatietherapie die bovendien vaak gedurende meerdere jaren word gegeven (tijdelijk) worden bespaard.

Aanvaardbaarheid, haalbaarheid en implementatie
De werkgroep voorziet geen problemen met aanvaardbaarheid, haalbaarheid of implementatie van de aanbevelingen.

Aanbevelingen
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Opmerkelijk is dat noch de dubbel blind gerandomiseerde fase 3 studie CheckMate 914 met de combinatie ipilimumab/nivolumab noch de Immotion010 met atezolizumab een DFS of OS voordeel heeft laten zien (references Pal & MotzeR). Alhoewel de studies niet direct vergelijkbaar zijn (atezolizumab is een PD-L1 inhibitor en nivolumab en ipilimumab werden gedurende 6 maanden gegeven) heeft dat de interpretatie van de toegevoegde waarde van pembrolizumab complexer gemaakt. Het is onder andere aanleiding geweest om niet op basis van 1 studie met alleen DFS voordeel over te gaan tot implementatie na het beschikbaar komen van het voorlopig positieve CieBOM advies. Nu er overlevingsvoordeel is aangetoond, moet deze beslissing worden herzien. Het overlevingsvoordeel dat is aangetoond is een 38% lager risico op overlijden bij patiënten behandeld met pembrolizumab ten opzichte van placebo. Tevens waren er na 24, 36 en 48 maanden meer patiënten in leven in de pembrolizumab groep dan in de placebo groep (2.4, 4.4 en 5.2 % respectievelijk). Niet iedereen waarbij in de placebo groep een recidief werd gevonden heeft alsnog een PD(L)1 remmer gehad. Dat is echter wel goed verklaarbaar. Immers, patiënten in de Keynote-564 hebben een veel intensiever radiologisch en laboratorium follow-up schema gehad. Hierdoor zijn er eerder aanwijzingen voor recidief ziekteactiviteit naar voren gekomen. Een aanzienlijk deel van deze groep zal vallen in de categorie favourable risk conform de IMDC risico classificatie en zal conform eerder richtlijnadvies met tyrosinekinase inhibitoren zijn behandeld. Tevens zal er een aanzienlijk deel bij het debuut van recidief ziekte slechts een beperkte tumorload hebben gehad waardoor zowel actieve surveillance als metastase gericht lokale therapie een optie zal zijn geweest.

Tegenover dit gunstige effect op de overleving moet worden afgewogen dat de events wat de overleving betreft ook na 4 jaar laag zijn (14%) en er een hoog risico van overbehandeling bestaat bij patienten met een laaggradige pT3a N0 M0 niertumor (zie NNT). Ook moet rekening worden gehouden met de NNH. Er is een toename in bijwerkingen gerapporteerd ten opzichte van placebo (20.7 vs 11.5 %) echter het verschil in graad 3-4 toxiciteit is aanzienlijk groter (18.6 vs 1.2%) In de Keynote-564 is geen letale toxiciteit gerapporteerd, maar de kans daarop zal niet onvermeld mogen blijven bij de counseling. Voorts zullen permanente bijwerkingen zoals hypothyreoidie en bijnierschorsinsufficiëntie (met de bijbehorende risico's) besproken moeten worden, waarvan de frequentie van die laatste

weliswaar laag is (1.2%), maar niet verwaarloosbaar. Verder is er onzekerheid over de vervolgtherapie bij patiënten die ook na pembrolizumab binnen 6 maanden een recidief ontwikkelen omdat deze patiënten niet meer voor combinatietherapie in aanmerking komen.

In de Keynote-564 studie mochten patiënten deelnemen met een heldercellig niercelcarcinoom met stadium pT2N0M0graad4; en de volgende categorieën ongeacht gradering van de tumor: pT3N0M0 en pT4N0M0, pT 1-4N+M0 of patiënten met M1 NED die zich presenteerden met gemetastaseerde ziekte waarbij zowel primaire tumor als metastasen verwijderd zijn. Vanuit de subgroepen in de KN-564 is helaas geen duidelijk onderscheid te maken bij welke patiënten categorie er een groter dan wel kleiner voordeel is dan het gemiddelde. Op basis van de studie gegevens is het daarom te adviseren om met deze patiënten na in opzet curatieve strategie de adjuvante behandeling met 17 cycli pembrolizumab 3-wekelijks 200 mg intraveneus te bespreken.

Overweeg en bespreek met patiënten 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 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).

Aanbeveling-2
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Het is belangrijk om in de selectie en bij de counseling van de patiënt een goede risico schatting te maken. Dit kan met name een uitdaging zijn in de groep patiënten met een pT3aN0M0 en lage gradering. Vaak gaat het om patiënten met een upstaging na minimaal invasieve chirurgie bij vermeende cT1b tumoren. Deze pT3a graad 1 tumoren hebben in verschillende retrospectieve studies een 5-jaar ziektevrije overleving van 79 t/m 82.1 % (Patel, 2020; Yim, 2021). Patiënt zal alvorens een besluit te kunnen nemen in het proces van gezamenlijke besluitvorming, op de hoogte gebracht moeten worden zowel over het risico op blijvende bijwerkingen, alsover de kans dat er weer recidief ziekteactiviteit op kan treden. Een hulpmiddel hiervoor kunnen web- based algoritmes zijn zoals bijvoorbeeld https://cancernomograms.com/nomograms/492. Dergelijke algoritmes zijn momenteel nog niet uitgerust om het specifieke overlevingsvoordeel weer te geven, maar kunnen wel een handvat bieden voor de risico inschatting voor bespreken van de kans op terugkeer ziekte activiteit van de maligniteit. Een vaak gebruikte risico score, de Leibovich score, werd bijvoorbeeld meerdere keren gevalideerd en geupdate en kan pT3a graad 1 tumoren op basis van necrose en omvang verder onderscheiden in laag-intermediar en intermediar risico.

Gebruik gevalideerde risico scores (bijvoorbeeld Leibovich) 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.

Aanbeveling voor M1 NED
Rationale van de aanbeveling: weging van de argumenten voor en tegen de interventie
In de Keynote-564patiënten studie werden ook patiënten met M1 NED geincludeerd. Dit waren voornamelijk patiënten die zich of presenteerden met primair (synchroon)

gemetastaseerde ziekte of waarbij de metastase binnen 1 jaar na de nefrectomie was opgetreden en verwijderd (metachrone metastasering). In meerdere nomogrammen voor de beslissing omtrend metastasectomie is een tijd tot recidief van minder dan 1 jaar een ongunstige factor (Tosco, 2013). Met name de metachroon gemetastaseerde subgroep binnen een jaar na nefrectomie heeft een hoog risico voor snelle ziekteprogressie. Het valt derhalve te overwegen beeldvorming na een interval van 3 maanden te herhalen om verdere ziekteprogressie uit te sluiten alvorens tot metastasectomie en mogelijk adjuvante therapie met pembrolizumab over te gaan

Overweeg bij patiënten met een heldercellig 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.

Kennislacunes

Het is onvoldoende bekend wie een recidief zal ontwikkelen en bij wie adjuvante therapie effectief zal zijn. TNM criteria hebben een slechte voorspellende waarde op recidief (prognostisch) en geen voorspellende waarde op effectiviteit van adjuvant pembrolizumab (predictief) . Recent zijn meerdere presentaties verschenen over het Kidney Injury Molecule-1 (KIM-1) wat mogelijk prognostisch en predictieve waarde heeft bij deze patiënten groep maar verder onderzoek is noodzakelijk.

Literatuur

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