Richtlijn
Diagnostiek en behandeling van bijniertumoren

INITIATIEF
Nederlandse Vereniging voor Heelkunde

IN SAMENWERKING MET
BijnierNET
Bijniervereniging NVACP
Nederlandse Internisten Vereniging
Nederlandse Vereniging voor Anesthesiologie
Nederlandse Vereniging voor Endocrinologie (Landelijke Werkgroep Endocrinologie Verpleegkundigen)
Nederlandse Vereniging voor Pathologie
Nederlandse Vereniging voor Radiologie
Nederlandse Vereniging voor Radiotherapie en Oncologie
Nederlandse Vereniging voor Urologie
Vereniging van Klinische Genetica Nederland

MET ONDERSTEUNING VAN
Kennisinstituut van de Federatie Medisch Specialisten

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

Colofon
RICHTLIJN

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Inhoudsopgave

Samenstelling van de werkgroep

Werkgroep

- Prof. dr. M.R. (Menno) Vriens, endocrien oncologisch chirurg, werkzaam in het UMC Utrecht te Utrecht, NVvH (voorzitter)
- Prof. dr. S. (Schelto) Kruijff, endocrien oncologisch chirurg, werkzaam in het UMCG te Groningen, NVvH (voorzitter)
- Prof. dr. R.A. (Richard) Feelders, internist-endocrinoloog, werkzaam in het Erasmus MC te Rotterdam, NIV
- Prof. dr. H.R. (Harm) Haak, internist, werkzaam in het Máxima MC te Eindhoven, NIV
- Drs. J.F. (Julia) Heusdens, anesthesioloog, werkzaam in het UMC Utrecht te Utrecht, NVA
- Prof. dr. R.R. (Ronald) de Krijger, patholoog, werkzaam in het UMC Utrecht/Prinses Máxima Centrum te Utrecht, NVVP
- Drs. J. (Jeroen) Vister, radioloog, werkzaam in het Universitair Medisch Centrum Groningen te Groningen, NVvR
- Dr. M.R. (Max) Dahele, radiotherapeut-oncoloog, werkzaam in het Amsterdam UMC te Amsterdam, NVRO
- Dr. J.F. (Hans) Langenhuijsen, uroloog, werkzaam in het Radboudumc te Nijmegen, NVU
- Dr. B.P.M. (Bernadette) van Nesselrooij, klinisch geneticus, werkzaam in het UMC Utrecht te Utrecht, VKGN
- J.G. (Johan) Beun, manager/coördinator BijnierNET, BijnierNET
- D.D. (Diana) Kwast-Hoekstra, MScN.RN. Verplegingswetenschapper en patientvertegenwoordiger, Bijniervereniging NVACP (tot 31-12-2022)
- Drs. N.T.M. (Nick) van der Meij, verpleegkundig specialist, werkzaam in het UMC Utrecht, te Utrecht, LWEV

<u>Met ondersteuning van</u>

- dr. A. (Anja) van der Hout, adviseur, Kennisinstituut van de Federatie Medisch Specialisten
- drs. S. (Sarah) van Duijn, adviseur, Kennisinstituut van de Federatie Medisch Specialisten
- drs. M. (Miriam) te Lintel Hekkert, adviseur, Kennisinstituut van de Federatie Medisch Specialisten
- drs. I. (Ingeborg) van Dusseldorp, medisch informatiespecialist, Kennisinstituut van de Federatie Medisch Specialisten

Startpagina – Diagnostiek en behandeling van bijniertumoren

Waar gaat deze richtlijn over?

De bijnier produceert essentiële hormonen. In de bijnier kunnen verschillende tumoren ontstaan, zoals feochromocytomen, aldosteron-, cortisol- of geslachtshormoonproducerende tumoren, metastasen en bijnierschorscarcinomen. Velen worden als incidentaloom gevonden. De behandeling vergt specifieke kennis en kunde van een multidisciplinair team. Kwaadaardige bijniertumoren hebben vaak een agressief biologisch gedrag en daarom is de juiste expertise van groot belang. Er bestaat (ongewenste) praktijkvariatie in de diagnostiek en behandeling van patiënten met een bijniertumor. Patiënten met een aandoening van de bijnier worden daardoor mogelijk niet altijd optimaal behandeld. Bovendien maken de lage incidentie van en de verscheidenheid aan bijniertumoren de zorg voor deze patiënten complex.

De richtlijn is gericht op de diagnostiek en behandeling van bijniertumoren, te weten: incidentaloom, aldosteronproducerend adenoom (ziekte van Conn), cortisolproducerend adenoom (syndroom van Cushing), feochromocytoom en adrenocorticaal carcinoom. Ook wordt aandacht besteed aan de behandeling van bijniermetastasen. De gemeenschappelijke factor is dat bij de meeste aandoeningen bijnierchirurgie noodzakelijk is. Viriliserende tumoren zijn buiten beschouwing gelaten, omdat op het gebied van deze tumoren in de praktijk geen knelpunten worden ervaren. De richtlijn heeft betrekking op zowel volwassenen als kinderen. Het neuroblastoom, een bijniertumor die bij kinderen voorkomt, is buiten beschouwing gelaten.

Voor wie is deze richtlijn bedoeld?

Deze richtlijn is bestemd voor alle zorgverleners die betrokken zijn bij de in de tweedelijnszorg voor patiënten met bijniertumoren, dat wil zeggen: chirurgen, endocrinologen, anesthesiologen, radiotherapeuten, pathologen, radiologen, klinisch genetici, urologen, verpleegkundigen, verpleegkundig specialisten en alle specialisten die incidenteel om specifieke redenen geconsulteerd worden.

Voor patiënten

De bijnier is een orgaan dat enkele belangrijke hormonen produceert. In de bijnieren kunnen verschillende goed- en kwaardaardige tumoren ontstaan die uiteindelijk tot een klachten kunnen leiden waardoor een operatie noodzakelijk is. Het doel van deze richtlijn is om te laten zien dat de behandeling van bijniertumoren specifieke kennis en kunde vergt en gedaan moet worden in een aantal centra die hierin gespecialiseerd zijn. In deze richtlijn is de aanbevolen diagnostiek en behandeling van deze tumoren wetenschappelijk onderbouwd. De richtlijn vormt een leidraad voor betrokken zorgprofessionals om iedere patiënt in Nederland met een bijniertumor de meest optimale en op maat gesneden zorg aan te bieden met de kennis die op de moment werelwijd voor handen is.

Er wordt informatie voor patiënten op www.thuisarts.nl ontwikkeld (is nog in ontwikkeling).

Hoe is de richtlijn tot stand gekomen?

Het initiatief van deze richtlijn is afkomstig van de Nederlandse Vereniging voor Heelkunde. De richtlijn is opgesteld door een multidisciplinaire commissie met vertegenwoordigers vanuit de Nederlandse Internisten Vereniging, Nederlandse Vereniging voor Anesthesiologie, Nederlandse Vereniging voor Endocrinologie (Landelijke Werkgroep Endocrinologie Verpleegkundigen), Nederlandse Vereniging voor Pathologie, Nederlandse Vereniging voor Radiologie, Nederlandse Vereniging voor Radiotherapie en Oncologie, Nederlandse

Vereniging voor Urologie, Vereniging van Klinische Genetica Nederland, BijnierNET en Bijniervereniging NVACP (Nederlandse Vereniging voor Addison en Cushing Patiënten).

Duurzaamheid
In 2024 is de Leidraad 'Duurzaamheid in richtlijnen: toevoegen van duurzaamheidsaspecten in richtlijnontwikkeling op de operatiekamer', op initiatief van de Nederlandse Vereniging voor Heelkunde, gepubliceerd. Als onderdeel hiervan zijn inhoudelijke duurzaamheidsmodules opgesteld door een multidisciplinaire werkgroep. Deze overkoepelende modules evalueren onderwerpen waarbij duurzaamheid een rol speelt. Hierbij worden alleen duurzaamheidsuitkomsten meegenomen.

De werkgroep van de richtlijn 'Diagnostiek en behandeling van bijniertumoren' onderschrijft het belang van duurzaamheid op de operatiekamer en ondersteunt de aanbevelingen uit de inhoudelijke richtlijnmodules. Toegespitst op de bijnierchirurgie:

- In de module 'Minimaal invasieve chirurgie' van deze richtlijn is gekeken naar verschillende operatietechnieken. Zie module 'Operatietechnieken' voor de duurzaamheidsaspecten m.b.t. de verschillende technieken.
- Conform module 'Reusables versus disposables' en module 'Afdekmaterialen', verzoekt de werkgroep om spaarzaam om te gaan met alle (afdek)materialen en indien mogelijk, zoveel mogelijk reusables te gebruiken.
- Voor bijnierchirurgie is operatiekamer klasse 1 afdoende. Indien mogelijk, minimaliseer het gebruik van luchtbehandeling op instellingsniveau, conform module 'Luchtbehandeling'.

Toepassen
Er is een stroomschema ontwikkeld behorende bij de module 'Aandacht bijnierschorsinsufficiëntie'. Deze is te vinden in de bijlage bij de betreffende module.

Status van de richtlijn
De richtlijn diagnostiek en chirurgische behandeling van bijniertumoren is opgenomen in het cluster endocriene tumoren en zal modulair worden herzien. Meer informatie over werken in clusters en modulair onderhoud vindt u hier.

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:	[datum]
Eerstvolgende beoordeling actualiteit	[datum] [en evt. de reden dat de herbeoordeling/herziening dan plaats zou moeten vinden].
Geautoriseerd door:	[Vereniging 1], initiatiefnemer [Vereniging 2], etc. [alle overige verenigingen (NB. Uitschrijven, geen afkortingen) en (patiënt) organisaties noemen die de richtlijn hebben geautoriseerd of geaccordeerd]
Belangrijkste wijzigingen t.o.v. vorige versie:	n.v.t.
Herbevestiging:	n.v.t.
Regiehouder(s):	Nederlandse Vereniging voor Heelkunde

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 en patiëntvertegenwoordigers (zie hiervoor de Samenstelling van de werkgroep) die betrokken zijn bij de zorg voor patiënten met bijniertumoren.

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
Vriens (voorzitter)	Chirurg UMC Utrecht	Bestuurslid NVvH (tot mei 2021)	Geen	Geen restricties

Kruijff (voorzitter)	Endocrien chirurg UMCG Groningen	Geen	Geen	Geen restricties
Feelders	- Professor - internist-endocrinoloog Erasmus MC - Adjunct Professor of Medicine New York University U.S.A.	- Medisch adviseur NVCAP, onbetaald - Bestuurslid Dutch Adrenal Network, onbetaald - Consultant Recordati, betaald	Geen	Geen restricties
Beun	Coordinator van de Stichting BijnierNET, parttime	Geen	Geen	Geen restricties
Langenhuijsen	Uroloog Radboudumc, Niijmegen	Bestuurslid Radboudumc Expertisecentrum Bijnierziekten Voorzitter eUROGEN WS 3 Rare genito-urological cancers en Expertise Area coordinator Adrenal tumours	ZonMw gefinancieerd onderzoek, DoelmatigheidsOnderzoek "Pentixafor PET/CT vs veneuze bijniervenesampling bij subtypering primair hyperaldosteronisme" i..s.m. PentixaPharm GmBH	Geen restricties
De Krijger	- Patholoog, UMC Utrecht, 0,2 fte - Patholoog, Prinses Maxima Centrum voor kinderoncologie, 0,7 fte	- Board member of Perined, Dutch organization supporting perinatal registries (vacatiegeld) - Council Member European Society of Pathology (onbetaald) - International Panel Member of Wilms tumor panel of SIOP Renal Tumor Study Group (onbetaald) - Chair International (European) pediatrie liver tumor panel	Geen	Geen restricties

		(PHITT trial) (onbetaald) - Chairmen Dutch/Belgian working group on Pediatrie Pathology (onbetaald) - Associate editor Pediatrie and Developmental Pathology (onbetaald) - Member editorial board Endocrine Pathology (onbetaald) - Member editorial board Virchows Archiv (onbetaald) - Member editorial board Frontiers in Endocrinology (onbetaald) - Editor-in-Chief Cancers, section Pediatrie Oncology (honorarium) - Member editorial board WHO Endocrine and Neuroendocrine Tumors, 5th edition (onbetaald)		
Heusdens	Anesthesioloog UMC Utrecht	Geen	Geen	Geen restricties
Haak	- Internist-endocrinoloog Maxima MC tot 01-09-2023, daarna nul-aanstelling en pensioen - Hoogleraar acute interne geneeskunde MUMC/UM, tot 01-02-2024	- Lid algemeen bestuurd BijnierNET - Voorzitter Bijniernetwerk Nederland D.A.N. - Raad van Toezicht Kempenhaeghe, betaald	Incidenteel grant van HRA	Geen restricties

Dahele	Radiotherapeut/VHD afdeling radiotherapie Amsterdam UMC (locatie VUmc)	Geen	Onderzoek financiering van: Varian Medical Systems (niet gerelateerd aan bijniertumoren)	Geen restricties
Van Nesselrooij	Klinisch Genetica, UMC Utrecht (0,8fte)	Secretaris van de VKGN (tot 01-01-2023)	Geen	Geen restricties
Kwast (tot 13-12-2022)	Bestuurslid Bijniervereniging NVACP te Nijkerk (onbetaald) (tot 13-12-2022)	Redactielid Bijniervereniging NVACP (onbetaald) (tot 13-12-2022)	Geen	Geen restricties
Vister	Radioloog, UMCG	Geen	Geen	Geen restricties
van der Meij	Verpleegkundig specialist AGZ, UMC Utrecht, afdeling Endocriene oncologie	Geen	Geen	Geen restricties

Inbreng patiëntenperspectief
Er werd aandacht besteed aan het patiëntenperspectief door Patiëntenfederatie Nederland, BijnierNET, Bijniervereniging NVACP, Nederlandse Federatie van Kankerpatiënten organisaties (NFK), Nierstichting, Nierpatiëntenvereniging Nederland uit te nodigen voor de invitational conference en afgevaardigden van BijnierNET en Bijniervereniging NVACP in de werkgroep. Het verslag van de invitational conference (zie bijlage) is besproken 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. De conceptrichtlijn is tevens voor commentaar voorgelegd aan de patiëntenorganisaties: Bijniervereniging NVACP, Patiëntenfederatie Nederland, BijnierNET, Nederlandse Federatie van Kankerpatiënten organisaties (NFK), Nierstichting, Nierpatiëntenvereniging Nederland, Nederlandse Hypofyse Stichting en de eventueel aangeleverde commentaren zijn bekeken en verwerkt.

Wkkgz & Kwalitatieve raming van mogelijke substantiële financiële gevolgen
Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz
Bij de richtlijn is conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uitgevoerd of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling zijn richtlijnmodules op verschillende domeinen getoetst (zie het stroomschema op de Richtlijnendatabase).

Uit de kwalitatieve raming blijkt dat er waarschijnlijk geen substantiële financiële gevolgen zijn, zie onderstaande tabel.

Module	**Uitkomst raming**	**Toelichting**
Module Diagnostiek morbus Conn	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.

Module Behandeling morbus Conn	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Behandeling Cushing	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Behandeling feochromocytoom	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Expertisecentrum ACC	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Biopsie bij ongedefinieerde retroperitoneale massa	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Kenmerken CT-scan incidentaloom	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Autonome cortisol (hyper)secretie (subklinische Cushing)	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Behandeling bijniermetastasen	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Minimaal invasieve chirurgie	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Genetisch testen en chirurgisch beleid	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Pathologieverslag	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.

Module Radiologieverslag	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Follow-up	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module Aandacht bijnierschorsinsufficiëntie	geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar is (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.

Werkwijze

AGREE

Deze richtlijnmodule is opgesteld conform de eisen vermeld in het rapport Medisch Specialistische Richtlijnen 2.0 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 bijniertumoren. Tevens zijn er knelpunten aangedragen door de NVvH, NVU, NOV, NVRO, VKGN, Bijniervereniging NVACP, IKNL, NAPA (vakgroep interne geneeskunde), Belangenvereniging Von Hippel-Lindau via een invitational conference. Een verslag hiervan is opgenomen in de bijlage.

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.

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.

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Module 1 – Diagnostiek bijnier incidentaloom

Uitgangsvraag
Wat is de optimale diagnostiek en follow-up van een gevonden bijnierincidentaloom op een CT-scan?

Inleiding
Op dit moment is er nog geen Nederlandse richtlijn beschikbaar die richting kan geven aan beleid en follow up met betrekking tot het bijnier incidentaloom. De prevalentie van gevonden incidentalomen in de populatie is aanzienlijk (tot 0.35-9% van alle abdominale CT scans, zelfs oplopend tot 10% in de oudere bevolking) en kan bovendien stijgen bij toename van beeldvorming (Sabet, 2016). Gezien het feit dat zowel beeldvormende studies nog steeds toenemen en dat er sprake is van toenemende vergrijzing, is de verwachting dat ook het aantal gevonden bijnierincidentalomen zal toenemen. Overdiagnostiek en overbehandeling van onterecht vermoedde maligniteit ligt hierbij op de loer. Definitieve preoperatieve diagnose van bijnierschorscarcinoom (ACC) is niet goed mogelijk enkel op basis van cytologie of biochemische testen. Het is daarom belangrijk aanknopingspunten voor een behandel- of vervolgbeleid te hebben op beeldvorming. In de literatuur worden specifieke criteria genoemd op CT en MRI welke meer voorspellend zijn voor een eventuele maligniteit. Deze module tracht de vraag te beantwoorden, welke 'imaging features' op CT belangrijk zijn om te onderscheiden bij het incidentaloom. Immers, tijdig uitsluiten van bijvoorbeeld een bijnierschorscarcinoom is van groot belang. Zo kan de groep patiënten met incidentalomen met suspecte kenmerken sneller worden gevonden en kan onnodige follow-up beeldvorming worden voorkomen bij incidentalomen met gunstige kenmerken.

Search and select
A systematic review of the literature was performed to answer the following question:
What is the diagnostic accuracy and effect on overall survival of a diagnostic model or multiple diagnostic factors on CT scan to diagnose malignancy in patients with an adrenal incidentaloma discovered on a CT?

P (Patients)	Patients with an incidentaloma suspected of malignancy discovered on a CT-scan and without prior history of malignancy
I (Intervention)	Diagnostic model or multiple diagnostic factors on CT-scan to diagnose malignancy of the adrenal incidentaloma
C (Control)	No use of a diagnostic model
R (Reference)	Histologic or pathological examination of the removed adrenal gland or follow-up (clinical or imaging)
O (Outcomes)	Overall survival, diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value, area under the ROC curve)

<u>Relevant outcome measures</u>
The guideline development group considered *overall survival, sensitivity* and *negative predictive value* as a critical outcome measure for decision making and *specificity* and *positive predictive value* and clinical outcomes as an important outcome measure for decision making.

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

The working group defined a maximum of ten patients per 1000 false negative as clinically (patient) important.
The working group defined the following difference as minimal clinically (patient) important difference regarding overall survival: An effect of >5% or >3% combined with HR<0.70 was considered clinically relevant (BOM, 2018)

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 18-8-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 218 hits. Studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICRO;
- The index test had to be as defined in the PICRO;
- One or more reported outcomes had to be as defined in the PICRO;
- Research type: Systematic review, randomized-controlled trial, observational cohort study, cross-sectional study
- Articles written in English or Dutch

21 studies were initially selected based on title and abstract screening. After reading the full text, eighteen studies were excluded (see the table with reasons for exclusion under the tab Methods), and three studies were included.

Results
Three studies were included in the analysis of the literature, one systematic review and two individual 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 tables.

Summary of literature
Description of studies
Sabet (2016) included 36 cohort studies in the systematic review however, regarding the scope of this review, only eleven studies which discussed patients without prior history of malignancy, were included (Birsen, 2014; Reginelli, 2014; Allan, 2013; Henning, 2009; Meyer, 2006; Mantero, 2000; Sworczak, 2000; Bergestrom, 2000; Kasperlik, 1997; Herrera, 1991; Hubbard, 1989). The cohort studies were included if the CT scan was discussed as diagnostic test, a gold standard test (operation, biopsy, Fine Needle Aspiration (FNA) or follow-up for more than six months) was performed, full explanation of the imaging procedure was present and a clear description of criteria for the index test with accepted thresholds was present. In total 1985 patients were included.
The included studies in the review described factors which diagnosed malignancy of the adrenal incidentaloma on the CT scan. Eleven studies described the factor size, three studies described the factor mass appearance and one study described the factor density. There were different reference tests used: Operation, follow-up, biopsy and FNA.
Sabet (2016) reported pooled estimates for sensitivity, specificity, positive and negative likelihood ratios for size cut-offs of the adrenal gland. Sabet (2016) also reported sensitivity, specificity, positive and negative likelihood ratios for different appearance characteristics and for different densities of the adrenal masses. Interestingly, they included a group of patients with a known malignancy.

Foo (2018) conducted a retrospective analysis with prospectively collected data from the Endocrine Surgery Database. Patients referred for evaluation of an AI in the period between

2004 and 2014 were included. Patients with symptoms presenting for investigation of adrenal tumors and patients with known extra-adrenal primary cancer screened for metastatic disease, were excluded. In total 96 patients were included in the study with a median age of 59 years and mean tumor diameter of 34mm. Foo (2018) performed a univariate analysis of factors associating with malignancy. Secondary, the diagnostic accuracy of the Scaled Score Algorithm, developed by the research group of the Cleveland Clinic, was measured. The Scaled Score Algorithm contains two factors: Tumor size and tumor density (Birsen, 2014). Both factors are scored. Tumor size <40 mm, between 40 and 60 mm or > 60 mm scored 1, 2 or 3 respectively. Tumor density on non-contrast CT <10 HU, between 10 and 20 HU and >20 HU scored 1, 2 or 3 respectively. Sum scores were calculated.
The reference test comprised histopathological examination for surgical cases or follow-up for at least six months for non-surgical cases.
The overall prevalence of malignancy in the study of Foo (2018) was 8%.
Foo (2018) calculated sensitivity, specificity and area under the ROC curve for the total algorithm score of 5 or higher.

Corwin (2022) performed a retrospective cohort study including data from six institutions in the United States between 2003 and 2017. Patients with the age of eighteen years or older who underwent an adrenal washout CT examination were included. In total 336 nodules in 299 patients were included in the analysis. There were no patient characteristics reported. The diagnostic accuracy of the factors nodule size (<4 cm versus ≥ 4 cm) and washout (presence versus absence of washout ≥ 60%) on CT was calculated.
The reference standard comprised different tests. At first, any available pathological specimen was used as reference standard. In absence of pathological specimens, an abdominal CT, chest CT, lumbar spine CT, lumbar spine MRI or PET/CT examinations performed at least one year before or after the washout CT examinations were used as reference standard. In patients with no pathology or image follow-up, medical records were reviewed to identify clinical notes.
The overall prevalence of malignancy in the study of Corwin (2022) was 1.5%.
Corwin (2022) calculated sensitivity, specificity, positive and negative predictive value of the factors washout and nodule size on CT.
It should be noted that the negative predictive value in this study described the predictive value of presence of adrenal malignancy. The positive predictive value described the predictive value of presence of benign nodules. A washout >60% and a nodule size of <4 cm were the chosen characteristics for absence of disease.

Results

Overall survival

No studies reported overall survival.

Diagnostic accuracy

Three studies reported diagnostic accuracy (Sabet, 2016; Foo, 2018; Corwin, 2022).

Sensitivity

All three studies reported sensitivity (Sabet, 2016; Foo, 2018; Corwin, 2022). The systematic review of Sabet (2016) reported sensitivity of different factors on CT: Tumor size, mass appearance, tumor density. Foo (2018) reported sensitivity of the Scaled Score Algorithm which includes the factors tumor size and tumor density. Corwin (2022) reported sensitivity of washout on CT (in combination with nodule size).
All results regarding sensitivity are summarized in table 1.

Table 1. Sensitivity regarding factors on CT for diagnosis of adrenal malignancy (Sabet, 2016; Foo, 2018; Corwin, 2022)

Study	Factor(s)	Sensitivity (95%CI)
Sabet (2016)	Cut-off 3 cm	0.91 (0.83-0.95) [a]
	Cut-off 4 cm	0.91 (0.82-0.96) [a]
	Cut-off 5 cm	0.78 (0.67-0.87) [a]
	Cut-off 6 cm	0.74 (0.63-0.82) [a]
	Tumor heterogeneity (3 studies included)	0.79 0.93 0.75
	Tumor irregularity (2 studies included)	0.41 0.50
	Tumor rough margin (1 study included)	0.56
	10 HU density (1 study included)	1
	16 HU density (1 study included)	0.95
	20 HU density (1 study included)	1
Foo (2018)	Scaled score algorithm (tumor size and tumor density)	0.75
Corwin (2022)	≥ 60% washout	0.75 (0.70-0.80) [b]
	≥ 60% washout and nodule size < 4 cm	0.77 (0.72-0.82) [b]
[a] Pooled data from SR; [b] diagnostic accuracy in nodules		

Negative Predictive Value (NPV)

One study reported NPV regarding factors on CT for diagnosis of adrenal malignancy (Corwin, 2022). Corwin (2022) reported a NPV for ≥ 60% washout on CT of 4.8% (95%CI 3.0-7.5) and a NPV for ≥ 60% washout and nodule size < 4 cm on CT of 1.4% (95%CI 1.1-1.8).

Specificity

All three studies reported specificity (Sabet, 2016; Foo, 2018; Corwin, 2022). The systematic review of Sabet (2016) reported specificity of different factors on CT: Tumor size, mass appearance, tumor density. Foo (2018) reported specificity of the Scaled Score Algorithm which includes the factors tumor size and tumor density. Corwin (2022) reported specificity of washout on CT (in combination with nodule size).
All results regarding sensitivity are summarized in table 2.

Table 2. Specificity regarding factors on CT for diagnosis of adrenal malignancy (Sabet, 2016; Foo, 2018; Corwin, 2022)

Study	Factor(s)	Specificity (95%CI)
Sabet (2016)	Cut-off 3 cm	0.44 (0.28-0.62) [a]
	Cut-off 4 cm	0.71 (0.55-0.83) [a]
	Cut-off 5 cm	0.82 (0.65-0.91) [a]
	Cut-off 6 cm	0.85 (0.69-0.94) [a]
	Tumor heterogeneity (3 studies included)	0.71 1 0.78
	Tumor irregularity (2 studies included)	0.93 0.98
	Tumor rough margin (1 study included)	0.90
	10 HU density (1 study included)	0.65
	16 HU density (1 study included)	1
	20 HU density (1 study included)	0.81
Foo (2018)	Scaled score algorithm (tumor size and tumor density)	0.87
Corwin (2022)	≥ 60% washout	0.80 (0.28-0.99) [b]
	≥ 60% washout and nodule size < 4 cm	1 (0.02-1) [b]
[a] Pooled data from SR; [b] diagnostic accuracy in nodules		

Positive Predictive Value (PPV)

One study reported PPV regarding factors on CT for diagnosis of adrenal malignancy (Corwin, 2022). Corwin (2022) reported a PPV for ≥ 60% washout on CT of 99.6 percent (95%CI 97.9-

99.9) and a PPV for ≥ 60% washout and nodule size < 4 cm on CT of 100% (95%CI not available).

Area under the ROC curve
One study reported Area under the ROC curve (AUC-ROC curve) for the diagnostic accuracy of the Scaled Score Algorithm including the factors tumor size and tumor density (Foo, 2018). Foo (2018) reported an AUC-ROC curve of 0.81 (95%CI 0.52-1.00).

Level of evidence of the literature
The level of evidence regarding the outcome measure **sensitivity** was downgraded to low GRADE because of study limitations (-1; risk of bias regarding possible selection bias and use of different reference standards in the studies), applicability (-1; bias due to indirectness because the systematic review included study populations with functional and non-functional tumors) and number of included patients (-1; imprecision because reported confidence intervals are wide intervals).

The level of evidence regarding the outcome measure **negative predictive value** was downgraded to low GRADE because of study limitations (-2; risk of bias regarding blinded test interpretation, use of different reference standards and flow and timing) and number of included patients (-1; imprecision because of small sample size).

The level of evidence regarding the outcome measure **specificity** was downgraded to low GRADE because of study limitations (-1; risk of bias regarding possible selection bias and use of different reference standards in the studies), applicability (-1; bias due to indirectness because the systematic review included study populations with functional and non-functional tumors) and number of included patients (-1; imprecision because of wide confidence intervals).

The level of evidence regarding the outcome measure **positive predictive value** was downgraded to low GRADE because of study limitations (-2; risk of bias regarding blinded test interpretation, use of different reference standards and flow and timing) and number of included patients (-1; imprecision because of small sample size).

The level of evidence regarding the outcome measure **area under the ROC curve** was downgraded to low GRADE because of study limitations (-2; risk of bias regarding unclear methods of index and reference test interpretation and flow and timing) and number of included patients (-1; imprecision because of small sample size).

Conclusions

No GRADE	No evidence was found regarding factors on CT scan on **overall survival** in patients with an adrenal incidentaloma found on the CT scan. *Source: -*

Low GRADE	The evidence suggests there is low confidence in the **sensitivity** regarding factors *tumor size, tumor heterogeneity, tumor irregularity, tumor margin, density and washout* on a CT-scan in differentiating malignancy from benignancy in patients with an adrenal incidentaloma. *Source: Sabet, 2016; Foo, 2018; Corwin, 2022*

Low GRADE	The evidence suggests there is low confidence in the **negative predictive value** regarding factors *tumor size and washout* on a CT-scan in differentiating malignancy from benignancy in patient with an adrenal incidentaloma. *Source: Corwin, 2022*

Low GRADE	The evidence suggests there is low confidence in the **specificity** regarding factors *tumor size, tumor heterogeneity, tumor irregularity, tumor margin, density and washout* on a CT-scan in excluding malignancy from benignancy in patients with an adrenal incidentaloma. *Source: Sabet, 2016; Foo, 2018; Corwin, 2022*

Low GRADE	The evidence suggests there is low confidence in the **positive predictive value** regarding factors *tumor size and washout* on a CT-scan in differentiating malignancy from benignancy in patient with an adrenal incidentaloma. *Source: Corwin, 2022*

Low GRADE	The evidence suggests there is low confidence in the **area under the curve** regarding factors *tumor size and density* on a CT-scan in differentiating malignancy from benignancy in patient with an adrenal incidentaloma. *Source: Foo, 2018*

Overwegingen – van bewijs naar aanbeveling

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

Uit de search kwam één systematic review naar voren (Sabet, 2016) die elf studies includeerde (Birsen, 2014; Reginelli, 2014; Allan, 2013; Henning, 2009; Meyer, 2006; Mantero, 2000; Sworczak, 2000; Bergestrom, 2000; Kasperlik, 1997; Herrera, 1991; Hubbard, 1989) en twee losse studies (Foo, 2018; Corwin, 2022).

De geïncludeerde studies hebben naar verschillende factoren op een CT-scan gekeken die onderscheid kunnen maken tussen maligniteit en een benigne bijnier incidentaloom. De factoren die de verschillende studies beschreven waren tumor grootte, tumor heterogeniteit, (on)regelmatigheid van de tumor, tumorbegrenzing, densiteit en washout op de CT-scan. Door de opzet van de geïncludeerde studies waarbij de systematic review zowel studies met functionele als niet-functionele tumoren includeerde, het gebruik van verschillende referentie testen en onduidelijkheid rondom test interpretatie en timing van de CT-scan en referentie test, is de bewijskracht laag. Dit betekent dat we niet zeker kunnen zijn over de uitkomsten van de studies.

Wanneer er naar de individuele factoren op de CT-scan wordt gekeken, laat de systematic review van Sabet (2016) een sensitiviteit van 0.91 (95%CI 0.83-0.95) voor tumor grootte van 3 centimeter en 0.91 (95%CI 0.82-0.96) voor tumor grootte van 4 centimeter zien. Voor deze tumor groottes is het betrouwbaarheidsinterval minder groot dan voor de sensitiviteit van tumor groottes 5 en 6 centimeter, 0.78 (0.67-0.87) en 0.74 (0.63-0.82) respectievelijk. Dit suggereert dat de zekerheid over de sensitiviteit van tumor grootte met het afkappunt 3 of 4 centimeter, groter is. Derhalve zou voor patiënten zonder bekende maligniteit in de

voorgeschiedenis een bijnierincidentaloom kleiner dan 4 cm met densiteit 10 HU of lager als benigne worden beschouwd. Interessant genoeg adviseren de auteurs in dit geval follow-up, zonder kenmerken te noemen die dermate bij een benigne laesie passen dat verdere follow-up achterwege kan worden gelaten. Voorbeelden hiervan zijn bijvoorbeeld een evident myelolipoom, lipide rijk adenoom of een cyste. Juist bij adequaat ontslag uit follow-up zou een kosten efficiënt beleid kunnen worden gevoerd. Ook de specificiteit voor maligne laesies stijgt sterk vanaf de gekozen drempelwaarde van 4 cm, hetgeen eerdere studies over deze waarde ondersteunde. De gevonden positieve en negatieve Likelyhood Ratio (LR) voor grootte blijken echter bevestigend noch uitsluitend voor maligniteiten, waardoor de auteurs ook reeds aangeven dat andere variabelen meegewogen zouden moeten worden voor een definitieve diagnose. Van deze variabelen lijkt de gemeten densiteit in Hounsfield Units (HU) hiervoor de sterkst bijdragende kandidaat. Voor deze meting dient een Region of Interest geplaatst te worden in een gebied 2/3 dat van het incidentaloom. De morfologie van de laesies zelf (heterogeniteit, marges, irregulaire vorm en calcificaties) toont minder significante Likelihood Ratio's. Dit wil zeggen dat bijvoorbeeld ook benigne incidentalomen een irregulaire vorm kunnen tonen of intralesionale calcificaties kunnen hebben. Wel komt in deze en ook andere studies naar voren dat een maximale diameter kleiner dan 4 cm in adrenale noduli een dermate lage kans geeft op maligne etiologie, dat men zou kunnen volstaan met follow-up. Dit bij een pretest kans op maligniteit van gemiddeld ongeveer 5% bij patiënten zonder oncologische voorgeschiedenis.
Daarnaast laten de geïncludeerde studies uit de review van Sabet (2016) die kijken naar tumor heterogeniteit een sensitiviteit zien van 0.79, 0.93 en 0.75 respectievelijk. De geïncludeerde studies uit de review van Sabet (2016) die kijken naar tumor densiteit laten een sensitiviteit zien van 1, 0.95 en 1 respectievelijk.

De studie van Foo (2018) die kijkt naar een algoritme om maligniteit te voorspellen neemt twee factoren mee: Tumor grootte en densiteit. Deze studie laat een sensitiviteit van 0.75 zien. Hiervoor werd een Cleveland Clinic risico stratificatie model toegepast. Het uiteindelijke voorkomen van een maligniteit in deze retrospectieve analyse van patiënten zonder maligniteit in de voorgeschiedenis was 8%. Definitieve preoperatieve diagnose van ACC is niet goed mogelijk op basis van cytologie of biochemie alleen, waardoor kenmerken als grootte en densiteit op CT belangrijke onderscheidende variabelen worden om de kans op een maligne proces in te schatten. Foo et al. sluiten aan bij recente richtlijnen welke een afkapwaarde van 4 cm suggereren voor chirurgische behandeling. Hormonaal actieve tumoren werden in deze studie geexcludeerd. Punten werden toegekend voor grootte (respectievelijk 1, 2 of 3 punten voor diameter >4, 4-6 of > 6 cm) en voor densiteit (respectievelijk 1, 2 of 3 punten voor densiteit op non-contrast CT <10 HU, 10-20 HU of >20 HU). Er werden geen maligniteiten geïdentificeerd bij scores 2 of 4. Een ACC liet echter een score van 3 zien, in scores 5 en 6 bestond een 27 % incidentie van ACC. Hoogste sensitiviteit (75%) en specificiteit (87 %) werd gevonden bij een afkapwaarde van 5. Daarnaast werd een associatie met een verhoogd risico op maligniteit gevonden bij heterogeniteit van het incidentaloom (p=0.0016) en een relatief washout percentage lager dan 40 % (p=0.0178). In verband met onjuiste classificatie van een ACC volgens het stratificatiemodel stelden auteurs voor het algoritme uit te breiden met een additionele parameter, waarvoor relatieve washout goed geschikt zou kunnen zijn. Dit komt overeen met de huidig voorgestelde Europese richtlijnen ESE en ENSAT, waarin bij niet discriminatoire kenmerken op blanco of post-contrast CT een bijnier-specifiek washout CT wordt geadviseerd (Fassnacht, 2016). Timing van deze CT is dan afhankelijk van de initiële grootte van de laesie.
Indien relatieve washout als factor wordt meegerekend, dient men wel in acht te nemen dat tumoren met grote gebieden van necrose of inliggende hemorrhagie een minder betrouwbaar contrast washout resultaat geven.

De studie van Corwin (2022) kijkt naar diagnostische accuratesse van factoren tumor grootte en washout voor onderscheid maken tussen maligniteit en benigniteit van de nodules. Deze studie rapporteerde een sensitiviteit van 0.75 (95%CI 0.70-0.80) zien voor de factor >60% washout en een sensitiviteit van 0.77 (95%CI 0.72-0.82) voor de factoren >60% washout en < 4 centimeter tumor grootte. De negatief voorspellende waarde die deze studie rapporteerde was voor beide (gecombineerde) factoren erg laag, 4.8% en 1.4% respectievelijk.

Ondanks de onzekerheid met betrekking tot de resultaten, komen de factoren tumor grootte (< 4 centimeter), tumor densiteit en tumor heterogeniteit wel vaker terug als sensitief als het gaat om onderscheid maken tussen maligniteit en benigniteit van een bijnier incidentaloom.

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

Wanneer evident sprake is van een benigne afwijking of maligne afwijking op basis van de gevonden kenmerken van het incidentaloom op CT, zal de verdenking hierop vaak de doorslag geven voor te voeren beleid. Het is uiteraard belangrijk eventuele follow-up beeldvorming, mogelijke chirurgie of juist ontslaan uit follow-up goed met patiënten te bespreken. Wanneer het een incidentaloom met aspecifieke kenmerken betreft, kan follow-up beeldvorming helpen in het stellen van een diagnose. In het geval dat meerdere modaliteiten mogelijk zijn, is het goed deze mogelijkheden in informed consent met de patiënt te bespreken. In sommige patiëntgroepen (kinderen, zwangeren) is het verstandig de stralingsbelasting via CT of PET zoveel mogelijk te beperken en voor een MRI scan te opteren als vervolg. Echter, sommige patiënten houden deze langere scanduur niet vol, of worden sterk gehinderd door claustrofobie. Andere opties tot beeldvorming kunnen dan wenselijker zijn.

Kosten (middelenbeslag)

Omdat de prevalentie van bijnierincidentalomen groot is en beeldvorming middels CT en/of MRI nog steeds toeneemt, zijn er voor zorgkosten belangrijke implicaties in het kiezen van een doelmatige strategie die onnodige diagnostiek of operaties voorkomt en toch de zeldzamere maligniteiten tijdig diagnosticeert. Daarnaast zou het voorkomen van onnodige stralenbelasting bij follow-up CT scans een rol moeten spelen in het kiezen van de juiste vervolg strategie. Chomsky-Higgins (2018) hebben gekeken naar de kosten en gezondheidsuitkomsten (in QALYs) voor verschillende surveillance strategieën bij patiënten met non-functionele incidentalomen kleiner dan 4 cm. Boven een 0.7% prevalentie voor adrenocorticaal carcinoom werd hierbij een eenmalige surveillance voor incidentalomen het meest effectief gevonden. Meer frequente follow-up leverde geen significante verbetering in Quality Adjusted Life Years (QALYs) en leidden tevens tot hogere kosten, hogere cumulatieve stralingsdoses en meer fout-positieve testuitslagen. Bij een significant percentage benigne laesies in incidentalomen onder 4 cm kan derhalve verminderde surveillance gesuggereerd worden. Voor oudere patiënten boven 60 jaar rapporteerden de auteurs zelfs afzien van verdere surveillance als meer kosteneffectieve strategie. Biochemische evaluatie kan onderdeel vormen van de eenmalige follow-up voor aspecifieke bijniernoduli. De ESE en ENSAT richtlijnen (2016) sluiten relatief reeds aan bij het beperkt houden van surveillance door een aanbeveling bij hormonaal inactieve laesies met densiteit lager dan 10 HU ongeacht grootte van verdere surveillance af te zien. Chomsky-Higgins (2018) gingen in hun studie intentioneel uit van een model dat de prevalentie van ACC hierbij overschat. Een lagere prevalentie is geassocieerd met geen surveillance als optimale strategie. Bij het bekende lage percentage voorkomen van maligniteiten onder incidentalomen in Nederland kunnen uitkomsten van de studie redelijkerwijs vertaald worden naar de Nederlandse zorg. In de toekomst zouden grote datasets verder kunnen helpen in het stratificeren van risicogroepen voor optimale vormgeving van follow-up.

Aanvaardbaarheid, haalbaarheid en implementatie

De geformuleerde aanbevelingen in deze module helpen om kenmerken op CT te identificeren welke differentiatie tussen benigne bijnierlaesies en maligniteiten vergemakkelijken. De werkgroep gaat hierbij uit van voldoende toegang tot CT in de algemene Nederlandse zorg. Parameters als grootte boven 4 cm, densiteitsmeting en evaluatie van washout zijn met de juiste instructies makkelijk toepasbaar. Gerichte aanbevelingen voor verdere follow-up moeten onnodige surveillance en onnodige operaties in deze grote groep voorkomen. De genoemde beeldvormende modaliteit en technieken zijn ook in niet-gespecialiseerde centra toepasbaar. Betreffende de meer-fasen bijnier CT zijn er in de literatuur sterk uiteenlopende protocollen te vinden, waardoor de beschikbare literatuur matig met elkaar te vergelijken is. In de aanbeveling worden meer voorkomende tempi na contrastbolus gehanteerd. Op basis van veel voorkomende selectiebias in oudere studies en gelimiteerde waarde van absolute washout boven 60% in de studie van Corwin, dient het kenmerk washout volgens de werkgroep met meer voorzichtigheid te worden geïnterpreteerd dan de kenmerken grootte en densiteit. Foo et al. rapporteren echter wel significante associatie van verhoogde kans op maligne laesies bij relatieve washout percentages lager dan 40%. De Europese ESE/ENSAT richtlijnen maken melding van de mogelijkheid tot het verrichten van washout CT bij persisterende onduidelijkheid op initiële CT, maar betrachten ook voorzichtigheid over de waarde van washout profielen, gebaseerd op de beschikbare literatuur (Fassnacht, 2016). Volgens de werkgroep zou de toegang tot (blanco) CT voor initiële risicostratificatie voor eenieder in Nederland gewaarborgd moeten zijn. Voor casus die overleg in een multidisciplinair team behoeven zou ook voldoende haalbaarheid moeten zijn in algemene Nederlandse ziekenhuizen. Bij hoge verdenking op ACC verdient het de voorkeur van de werkgroep betreffende casus vanwege het zeldzame voorkomen hiervan, te verwijzen naar hierin gespecialiseerde centra. De in deze richtlijn genoemde afkappunten op CT maken reeds langere tijd deel uit van het repertoire van de opleiding Radiologie. Betere bekendheid met geldende richtlijnen zou kunnen helpen de toepassingen in standaard verslaglegging te vergroten.

Hoewel de toegankelijkheid van CT als beeldvormende modaliteit, en de hoge spatiele resolutie dit vaak de gekozen scan maakt om bijnierlaesies te karakteriseren, kunnen ook andere modaliteiten een toegevoegde waarde hebben in deze evaluatie. Voorbeelden hiervan zijn MRI en FDG-PET. Voor kinderen en zwangeren is MRI zelfs als eerste keus scan te overwegen, gezien men onnodige stralingsdosis wil voorkomen. Signaalverlies door een chemical shift artefact op een uit-fase MRI scan kan helpen een vetrijk adenoom te diagnosticeren. Visueel vergelijk van in- en uit-fase scans is vaak voldoende om een mogelijk adenoom op te merken. Ook hier zijn echter fout-positieve resultaten beschreven, waarbij vethoudende metastasen van bijvoorbeeld een hepatocellulair carcinoom of een renaal cel carcinoom een adenoom kunnen nabootsen. De sensitiviteit van MRI blijkt hoger bij HU-waarden onder de 30.

Aanbeveling

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

Bij detectie van een bijnierincidentaloom is het van belang te duiden of men met een benigne of maligne entiteit te maken heeft, ook om onnodige en kostbare follow-up te voorkomen wanneer het een benigne laesie betreft. Dergelijke follow-up kan ook leiden tot angst en onzekerheid bij de patiënt. Een zeldzame maligniteit als ACC heeft echter vaak een slechte prognose en dient zonder uitstel gedetecteerd en geopereerd te worden. Vaak heeft de radioloog bij afwezigheid van hieraan gerelateerde klachten, een poortwachtersfunctie in de detectie en adequate beschrijving van deze laesies. Kenmerken als grootte, densiteit en -

indien verricht- washout dienen dan ook nauwkeurig in het radiologisch verslag genoemd te worden. Indien beleid rondom een incidentaloom bediscussieerd dient te worden, verdient het de voorkeur dit in een multidisciplinair team te doen. Essentieel hierin zijn de endocrinoloog, chirurg, radioloog en patholoog.

Omdat veruit de meeste bijnierincidentalomen vetrijke adenomen betreffen, zal vaak kunnen worden volstaan met een blanco CT opname. Veel van deze laesies worden al gedetecteerd op index beeldvorming, welke om andere klinische redenen wordt vervaardigd, bijvoorbeeld een CT thorax. Een densiteit < 10 HU is hoog specifiek voor het lipide rijk adenoom (98%), waardoor men, zeker bij beperkte grootte mag uitgaan van een benigne laesie. Ongeveer 30% van de adenomen is echter lipide arm, waardoor er in densiteit een overlap kan bestaan met andere laesies, zoals ACC en feochromocytoom. Bij kleine bijniernoduli (1-2 cm) kan worden overwogen deze middels een enkele scan (6-12 maanden na detectie) te vervolgen om te controleren op eventuele groei. Bij grotere bijnierlaesies en onzekere kenmerken verdient beeldvormende follow-up op kortere termijn middels een meer-fasen CT de voorkeur. Hoewel protocollen hiervoor verschillen bestaat de meest geijkte methode hiervoor uit drie scanfasen: een blanco CT, een CT 60-90 seconden na contrastbolusinjectie en een late contrastfase na 15 minuten. Eventuele washoutprofielen kunnen ondersteunend zijn in het bevestigen danwel uitsluiten van een maligniteit. Men dient echter rekening te houden met het feit dat de waarde van washout bij homogene noduli > 10 HU in patiënten zonder een bekende maligniteit in de voorgeschiedenis relatief beperkt is (Corwin et al. 2022). Eerdere studies die over washout van bijnierincidentalomen rapporteerden lijken onderhevig aan een selectie bias door de inclusie van ook patiënten met bekende metastasen. Hierdoor is de gerapporteerde prevalentie van maligne noduli mogelijk niet representatief voor de prevalentie van dergelijke maligniteiten in de algehele populatie (zonder kanker). Daarnaast is in kleinere noduli de waarde van washout beperkter en het risico op foute meetwaarden groter. Ook Sabet et al. rapporteren lage positieve en negatieve Likelihood Ratios voor washout van bijnier noduli. De werkgroep beschouwt multi-fase washout CT derhalve als een mogelijkheid tot vervolg beeldvorming, maar erkent dat deze methode beperkingen heeft, voor zowel relatieve als absolute contrast washout.

Recentelijk is de waarde van FDG-PET in de risicostratificatie voor bijnierincidentalomen erkend. Salgues et al. (2021) rapporteren een sensitiviteit van 90%, een specificiteit van 92.6%, een PPV van 69.2% en een NPV van 98%, waarmee wordt ondersteund dat afwezigheid van verhoogde FDG-uptake maligniteiten goed kan uitsluiten. Uit deze en andere studies blijkt echter ook de mogelijkheid tot fout-positieven, waardoor conclusies over FDG-PET beelden preferentieel bezien moeten worden in combinatie met uitslagen van andere diagnostische testen. Voor zowel MRI als FDG-PET geldt dat gezien de lage aantallen in gerapporteerde studies de bewijskracht nog relatief lager ligt en de werkgroep aanraadt uitslagen hiervan in een shared decision proces te bespreken. Deze technieken kunnen wel een alternatief zijn voor wash-out CT scans bij aspecifieke incidentalomen groter dan 1 cm. Karakteristieken van deze overige beeldvormende technieken vallen echter buiten het bestek van deze module en uitgangsvraag.

In een recente update van de ESE richtlijn van Fassnacht et al. (2023) wordt meer gewicht toegekend aan een densiteit onder de 10 HU, en is het afkappunt van 4 cm in diameter minder leidend. De werkgroep onderstreept deze aanbevelingen. Wel kan de grens van 4 cm nog gebruikt worden om patiëntgroepen te stratificeren met bijniernoduli welke een densiteit tonen van 11-20 HU. Bij de kleinere noduli van 1 tot 4 cm kan direct aanvullende beeldvorming in de vorm van FDG-PET, meerfasen CT of MRI helpen te differentieren. De keuze voor het type beeldvorming kan afhankelijk van lokale ervaring en voorkeur. Meer dan 90%

incidentalomen in deze groep zijn ook benigne. Additioneel kan follow-up CT of MRI worden ingezet na 6-12 maanden. Bij groei van meer dan 20% (tenminste meer dan 5 mm) wordt overleg in een MDO geadviseerd. Daarentegen kan bij afwezigheid van groei de patiënt worden ontslagen uit beeldvormende follow-up. De bewijskracht voor aanhoudende interval follow-up geadviseerd in de nieuwe Europese richtlijn is laag. Rekening houdend met stijgende zorgkosten en toekomstig mogelijk beperktere scancapaciteit in de Nederlandse situatie vindt de werkgroep het derhalve te verdedigen eventuele follow-up bij groei minder dan 20% kritisch te bezien, en waar nodig te overleggen binnen een MDO.

Hoewel specifieke endocrinologische work-up buiten het bestek van deze module valt vindt de werkgroep het belangrijk te benadrukken bij iedere patiënt met een incidentaloom groter dan 1 cm biochemische evaluatie te verrichten en klinisch onderzoek te doen naar tekenen van hormonale overproductie. Bij hormonaal actieve incidentalomen en klinische afwijkingen wordt bespreking binnen een MDO geadviseerd, wanneer chirurgie wordt overwogen. Bij milde autonome cortisol secretie (MACS), gedefinieerd als cortisol concentratie boven 50nmol/L na een 1 mg Dexamethason suppressie test zonder klinisch kenmerken van Cushing, wordt vervolg door de endocrinoloog geadviseerd.

Aangezien in meerdere gevallen initiële detectie van de betreffende incidentalomen plaats zal vinden op een CT na contrast (meestal portoveneuze contrastfase) zullen grootte en densiteit bepalen of verder vervolg in de vorm van een specifieke vervolgscan nodig zal zijn. De radioloog kan hierbij verder adequate zorg helpen stroomlijnen door gebruik te maken van gestandaardiseerde verslaglegging (zie module ‘Radiologieverslag’), waarin duidelijke vermelding van kenmerken die een maligniteit uitsluiten of meer waarschijnlijk maken, van belang zijn.

Bij de volgende aanbevelingen wordt uitgegaan van >1 cm bijnierincidentaloom in een patiënt zonder oncologische voorgeschiedenis.

- Verricht biochemische evaluatie van ieder incidentaloom en laat patiënt klinisch onderzoeken door endocrinoloog en bij afwijkingen vervolgen.

- Laat verdere beeldvormende follow-up achterwege, indien het incidentaloom evident benigne karakteristieken heeft (overwegend macroscopisch vet, densiteit < 10 HU of benigne calcificatie) en kleiner is dan 4 cm.

- Evalueer of het incidentaloom groei vertoont, wanneer oude beeldvorming beschikbaar is. Bij onveranderde diameter/volume > 1 jaar en benigne kenmerken kan verdere follow-up achterwege worden gelaten.

- Beschouw aspecifieke bijniernoduli van 1-2 cm als meest waarschijnlijk benigne. Overweeg bij HU 11-20 en afmeting 1-4 cm aanvullende FDG-PET, meerfasen CT of verricht follow-up CT danwel MRI na 1 jaar. Bij kinderen en zwangeren is MRI te prefereren.

- Bespreek in multidisciplinair overleg bij groei meer dan 20% (tenminste 5 mm), HU >20, of diameter > 4 cm en HU 11-20 van de bijnierlaesie.

- Beslis samen met de patiënt of overgegaan kan worden tot adrenalectomie wanneer een niet-hormonaal actief incidentaloom groter is dan 4 cm, afhankelijk

van klinische symptomen en verdere beeldvormende kenmerken als densiteit, heterogeniteit en necrose.

- Bespreek in multidisciplinair overleg bij verdenking op maligniteit, indien het incidentaloom hormonaal actief is en/of chirurgie wordt overwogen. Voer dit overleg bij voorkeur in hierop gespecialiseerde (bijnierschorscarcinoom) centra.

- Zie stroomschema Diagnostiek

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Bijlagen bij Diagnostiek bijnier incidentaloom

Evidence tables

Evidence table for diagnostic test accuracy studies

Research question: What is the diagnostic accuracy and effect on overall survival of a diagnostic model or multiple diagnostic factors on CT scan to diagnose malignancy in patients with an adrenal incidentaloma discovered on a CT?

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Sabet, 2016	Systematic review of cohort studies *Literature search up to January 2016* **A**: Birsen, 2014 **B**: Reginelli, 2014 **C**: Allan, 2013 **D**: Henning, 2009 **E**: Meyer, 2006 **F**: Mantero, 2000 **G**: Sworczak, 2000 **H**: Bergestrom, 2000	Inclusion criteria SR: - Original articles - Published after 1970 in English - Discussed CT scan as diagnostic test - Gold standard test (operation, biopsy, FNA or follow-up for more than 6 months) was performed - Presence of full explanation of imaging procedure that follows standard	Describe index factors: Size (11 studies), mass appearance (3 studies), density (1 study)	Describe reference test[1]: **A**: Operation, follow-up **B**: Operation, follow-up **C**: Operation **D**: Operation, follow-up **E**: Operation **F**: Operation **G**: Operation **H**: Operation, biopsy **I**: Operation (>4 cm), biopsy **J:** Operation, FNA, follow-up **K**: Operation, FNA, follow-up Prevalence (%) [based on refence test at specified cut-off point]: Not reported	Endpoint of follow-up: Not reported For how many participants were no complete outcome data available: Not reported	Outcome measures and effect size (include 95%CI and p-value if available)[4]: <u>Outcome measure-1</u> Defined as LR for size: Pooled estimate of sensitivity, specificity, positive and negative LR for different size cut-offs of the adrenal gland mass: **Cut-off 3 cm** Co-sensitivity [95% CI]: 0.91 [0.83-0.95] Co-specificity [95% CI]: 0.44 [0.28-0.62] Pooled positive LR [95% CI]: 1.6 [1.2-2.2] Pooled negative LR [95% CI]: 0.21 [0.10-0.42]	<u>Study quality (ROB):</u> QUADAS score (out of 14) **A**: 13 **B**: 11 **C**: 12 **D**: 13 **E**: 12 **F**: 11 **G**: 12 **H**: 11 **I**: 12 **J:** 12 **K**: 12 <u>Authors conclusion:</u> As a conclusion, an evidence-based flowchart is suggested in which among the patients without history of malignancy adrenal masses smaller than 4 cm or the ones larger than 4

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
	I: Kasperlik, 1997 **J:** Herrera, 1991 **K**: Hubbard, 1989 <u>Design and country:</u> **A**: Retrospective cohort study, USA **B**: Retrospective cohort study, Italy **C**: Prospective cohort study, USA **D**: Retrospective and prospective cohort study, Sweden **E**: Retrospective cohort study, Germany **F**: Retrospective cohort study, Italy **G**: Prospective cohort study, Poland	method of CT scanning - Presence of clearly described criteria for index test with accepted thresholds Exclusion criteria SR: - Articles overlapping with others - Articles without any case of malignancy or benign mass - Case report or case series articles *36 studies included* <u>Important patient characteristics at baseline</u>: <u>Number of patients, mean</u>				**Cut-off 4 cm** Co-sensitivity [95% CI]: 0.91 [0.82-0.96] Co-specificity [95% CI]: 0.71 [0.55-0.83] Pooled positive LR [95% CI]: 3.1 [2-4.9] Pooled negative LR [95% CI]: 0.13 [0.06-0.25] **Cut-off 5 cm** Co-sensitivity [95% CI]: 0.78 [0.67-0.87] Co-specificity [95% CI]: 0.82 [0.65-0.91] Pooled positive LR [95% CI]: 4.3 [2.1-8.9] Pooled negative LR [95% CI]: 0.26 [0.16-0.44] **Cut-off 6 cm** Co-sensitivity [95% CI]: 0.74 [0.63-0.82] Co-specificity [95% CI]: 0.85 [0.69-0.94] Pooled positive LR [95% CI]: 5.0 [2.4-10.8] Pooled negative LR [95% CI]: 0.31 [0.22-0.43] <u>Outcome measure-2</u> Defined as LR for mass appearance: Sensitivity, specificity, positive and negative LR for different	cm with density of less than 10 HU can be just followed up but the lesions larger than 4 cm with density more than 10 HU should be gone under additional diagnostic procedure. Different appearances of the mass do not show a potent positive or negative LR.

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
	H: Prospective cohort study, Sweden **I**: Prospective cohort study, Poland **J:** Retrospective cohort study, USA **K**: Retrospective cohort study, USA <u>Funding and conflicts of interest:</u> Authors of the review declare to have no competing interests.	<u>age (range) in years:</u> **A**: N=157, NR **B**: N=35, NR (25-89) **C**: N=49, 51 (NR) **D**: N=38, 67.5 (45-81) 60 (24-77) **E**: N=52, 56.4 (NR) **F**: N=1004, 58 (15-86) **G**: N=57, 54.7 (34-79) **H**: N=15, NR (42-78) **I**: N=208, 52 (14-76) **J:** N=342, 62 (2-86) **K**: N=28, NR (22-74) <u>Description of the mass:</u> **A**: Non-functional **B**: Non-functional **C**: Functional **D**: Non-functional **E**: Non-functional				appearance characteristics of the adrenal mass: **Heterogeneity (3 included studies)** Sensitivity: 0.79; 0.93; 0.75 Specificity: 0.71; 1; 0.78 Positive LR: 2.72; ∞ ; 3.4 Negative LR: 0.29; 0.07; 0.32 **Irregularity (2 studies included)** Sensitivity: 0.41; 0.50 Specificity: 0.93; 0.98 Positive LR: 5.85; 0.45 Negative LR: 0.63; NR **Rough margin (1 study included)** Sensitivity: 0.56 Specificity: 0.90 Positive LR: 5.6 Negative LR: 0.48 <u>Outcome measure-3</u> Defined as LR for mass density: Sensitivity, specificity, positive and negative LR for different densities of the adrenal mass: **10 HU (1 study included)** Sensitivity: 1 Specificity: 0.65	

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
		F: Non-functional **G**: Non-functional **H**: >1 cm functional, non-functional **I**: Non-functional **J:** Non-functional **K**: Non-functional				Positive LR: 2.85 Negative LR: 0 **16 HU (1 study included)** Sensitivity: 0.95 Specificity: 1 Positive LR: ∞ Negative LR: 0.05 **20 HU (1 study included)** Sensitivity: 1 Specificity: 0.81 Positive LR: 5.26 Negative LR: 0	
Foo, 2018	Type of study[2]: Retrospective analysis of prospective cohort Setting and country: Single center study, Australia Funding and conflicts of	Inclusion criteria: - Consecutive patients referred for evaluation of AI between 2004 and 2014 Exclusion criteria: - Symptomatic patients presenting for	Describe index factors: Age, gender, previous history of malignancy, tumor size, density, percentage washout on contrast CT, mass appearance, calcification on CT and cortisol levels Description of Scaled Score Algorithm published by research group from the Cleveland Clinic:	Describe reference test[3]: Histopathology for surgical cases or follow-up for at least six months. Cut-off point(s): Not reported	Time between the index test and reference test: Depending on reference test (follow-up at least six months) For how many participants were no complete outcome data available: N=32 (33%) ○ N=23: Not both size and density measurements on CT	Outcome measures and effect size (include 95%CI and p-value if available)[4]: <u>Diagnostic accuracy Scaled Score Algorithm:</u> Score 5-6: N=11 (17%) Sensitivity: 75% Specificity: 87% Area under ROC curve [95% CI]: 0.81 [0.52-1.00]	<u>Authors conclusion:</u> We propose that a combination of variables, including size, density and percentage washout on contrast CT, need to be included in order to improve on current risk stratification models for the management of AI. Factors age, gender, history of malignancy, tumor size, density, percentage

[2] In geval van een case-control design moeten de patiëntkarakteristieken per groep (cases en controls) worden uitgewerkt. NB; case control studies zullen de accuratesse overschatten (Lijmer et al., 1999)

[3] De referentiestandaard is de test waarmee definitief wordt aangetoond of iemand al dan niet ziek is. Idealiter is de referentiestandaard de Gouden standaard (100% sensitief en 100% specifiek). Let op! dit is niet de “comparison test/index 2”.

[4] Beschrijf de statistische parameters voor de vergelijking van de indextest(en) met de referentietest, en voor de vergelijking tussen de indextesten onderling (als er twee of meer indextesten worden vergeleken).

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
	interest: Not reported	investigation of adrenal tumors - Patients with known extra-adrenal primary cancer screened for metastatic disease N=96 Prevalence:8.2% Median age in years (range): 59 (25-77) Sex: 48% male / 52% female Other important characteristics: Mean tumor diameter in mm (SD): 34 (18.8)	Tumor size <40, 40-60 or >60 mm scored 1,2 or 3 respectively. Tumor density on non-contrast CT <10 HU, 10-20 HU or >20 HU scored 1, 2 or 3. Cut-off point(s): Sensitivity, specificity and positive likelihood ratios were calculated for total score cut-off 5.		○ N=9: Hormonally active tumors		washout on contrast CT, mass appearance, calcification on CT and cortisol levels are in the univariate analysis and therefore results are not displayed.
Corwin, 2022	Type of study: Retrospective cohort study Setting and country: Six	Inclusion criteria: - Patients 18 years or older who underwent adrenal	Describe index factors: Nodule size (<4 cm versus ≥ 4 cm) and washout (presence versus absence of washout ≥ 60%) Cut-off point(s):	Describe reference test: • Any available pathologic specimen from surgical resection or	Time between the index test and reference test: Not reported For how many participants were no complete outcome	Outcome measures and effect size (include 95%CI and p-value if available): <u>Diagnostic performance of 60% washout or more for</u>	<u>Authors conclusion:</u> Our findings suggest that washout CT has limited utility in the evaluation of incidental adrenal nodules smaller than 4 cm in

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
	institutions, United States Funding and conflicts of interest: The author declares there are no disclosures relevant to the subject matter of this article	washout CT examination - CT examinations between 2003 and 2017 Exclusion criteria: - CT report did not describe adrenal nodules or nodules measuring less than 1 cm in short-axis diameter - History of malignancy or clinical suspicion for a functional adrenal tumor at time of washout CT - Clear evidence of metastatic malignancy on washout CT - Artifact on washout CT - Adrenal nodule characteristics: Unenhanced	See above for cut-off points for different factors.	percutaneous biopsy • In absence of pathologic specimen: Abdominal CT, chest CT, lumbar spine CT, lumbar spine MRI or PET/CT examinations performed at least one year before or after the washout CT examinations • In patients with no pathology or image follow-up or indeterminate growth rate (4-7 mm per year) EMR was reviewed to identify clinical notes Cut-off point(s): Benignancy was defined as either no change in size or growth of 3 mm per year or less. Malignancy was defined as growth of 8 mm per year or more.	data available: No missing data reported.	<u>differentiating benign versus malignant nodules:</u> Sensitivity: 75.5% (95%CI 70.4-80.1) Specificity:80% (95%CI 28.4-99.5) PPV: 99.6% (95%CI 97.7-99.9) NPV: 4.8% (95%CI 3.0-7.5) <u>Diagnostic performance of 60% washout or more and nodules < 4 cm for differentiating benign versus malignant nodules:</u> Sensitivity: 77.5% (95%CI 72.4-82.1) Specificity:100% (95%CI 2.5-100) PPV: 100% (95%CI NA) NPV: 1.4% (95%CI 1.1-1.8)	patients without known malignancy. Very low prevalence of malignancy and therefore wide confidence intervals regarding specificity and positive predictive value (PPV). Pheochromocytoma's were excluded from the diagnostic performance analysis.

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
		attenuation < 10 HUR, absence of enhancement > 10 HU, heterogeneity on unenhanced images, other suspicious features including cystic or necrotic appearance - No reference standard available N= 336 nodules (in 299 patients) Prevalence: N=5 (1.5%) No patient characteristics reported.		In patients with no pathology or image follow-up or indeterminate growth rate (4-7 mm per year) EMR was reviewed to identify clinical notes. Benignancy was defined as no clinical evidence of adrenal malignancy documented at least 5 years after the wash-out CT examination.			
∞ Indicates significantly high positive LR							

Risk of bias tables

Table of quality assessment for systematic reviews of diagnostic studies

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

Research question: What is the diagnostic accuracy and effect on overall survival of a diagnostic model or multiple diagnostic factors on CT scan to diagnose malignancy in patients with an adrenal incidentaloma discovered on a CT?

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Assessment of scientific quality of included studies?[5] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[6] Yes/no/unclear	Potential risk of publication bias taken into account?[7] Yes/no/unclear	Potential conflicts of interest reported?[8] Yes/no/unclear
Sabet, 2016	Yes	Yes	No, no description of excluded studies	No, no clear description of prevalence, incomplete outcome data and end-point of follow-up	Yes, QUADAS	Unclear, individual study populations included functional and non-functional tumors	No	No, no potential conflicts of interest reported of individual studies

Risk of bias assessment diagnostic accuracy studies (QUADAS II, 2011)

Research question: What is the diagnostic accuracy and effect on overall survival of a diagnostic model or multiple diagnostic factors on CT scan to diagnose malignancy in patients with an adrenal incidentaloma discovered on a CT?

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Foo, 2018	Was a consecutive or random sample of patients enrolled? Unclear, due to single-center study a selection bias might have occurred Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear, no specification of interpretation method of index test. If a threshold was used, was it pre-specified? Yes, tumor size and density thresholds were specified	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear, no specification of interpretation method of reference test	Was there an appropriate interval between index test(s) and reference standard? Unclear, no definitions of intervals Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No Were all patients included in the analysis? No, but clear reasons for exclusion	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: UNCLEAR**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: UNCLEAR**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: UNCLEAR**	CONCLUSION Could the patient flow have introduced bias? **RISK: HIGH**	
Corwin, 2022	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? No, only the first investigator at each institution reviewed both the adrenal washout CT examinations and reference standard If a threshold was used, was it pre-specified? Yes	Is the reference standard likely to correctly classify the target condition? Unclear, different reference standards were used. Were the reference standard results interpreted without knowledge of the results of the index test? Unclear	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No Were all patients included in the analysis? No, patients with pheochromocytomas were excluded from the analysis.	Are there concerns that the included patients do not match the review question? Unclear, no patient characteristic reported Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: LOW**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: HIGH**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: HIGH**	CONCLUSION Could the patient flow have introduced bias? **RISK: HIGH**	

Table of excluded studies

Reference	Reason for exclusion
Marty M, Gaye D, Perez P, Auder C, Nunes ML, Ferriere A, Haissaguerre M, Tabarin A. Diagnostic accuracy of computed tomography to identify adenomas among adrenal incidentalomas in an endocrinological population. Eur J Endocrinol. 2018 May;178(5):439-446. doi: 10.1530/EJE-17-1056. Epub 2018 Feb 21. PMID: 29467231.	Wrong target condition: Diagnosis of benign adrenal incidentalomas
Cho YY, Suh S, Joung JY, Jeong H, Je D, Yoo H, Park TK, Min YK, Kim KW, Kim JH. Clinical characteristics and follow-up of Korean patients with adrenal incidentalomas. Korean J Intern Med. 2013 Sep;28(5):557-64. doi: 10.3904/kjim.2013.28.5.557. Epub 2013 Aug 14. PMID: 24009451; PMCID: PMC3759761.	Wrong study population: Nonfunctional and functional adrenal incidentalomas
Moawad AW, Ahmed A, Fuentes DT, Hazle JD, Habra MA, Elsayes KM. Machine learning-based texture analysis for differentiation of radiologically indeterminate small adrenal tumors on adrenal protocol CT scans. Abdom Radiol (NY). 2021 Oct;46(10):4853-4863. doi: 10.1007/s00261-021-03136-2. Epub 2021 Jun 3. PMID: 34085089.	Wrong study population: Indeterminate incidentalomas
Wale DJ, Wong KK, Viglianti BL, Rubello D, Gross MD. Contemporary imaging of incidentally discovered adrenal masses. Biomed Pharmacother. 2017 Mar;87:256-262. doi: 10.1016/j.biopha.2016.12.090. Epub 2017 Jan 4. PMID: 28063406.	Wrong study design
Dinnes J, Bancos I, Ferrante di Ruffano L, Chortis V, Davenport C, Bayliss S, Sahdev A, Guest P, Fassnacht M, Deeks JJ, Arlt W. MANAGEMENT OF ENDOCRINE DISEASE: Imaging for the diagnosis of malignancy in incidentally discovered adrenal masses: a systematic review and meta-analysis. Eur J Endocrinol. 2016 Aug;175(2):R51-64. doi: 10.1530/EJE-16-0461. Epub 2016 Jun 2. PMID: 27257145; PMCID: PMC5065077.	Wrong tests: MRI, PET and wrong target condition: Detection ACC or adrenal metastases
Kahramangil B, Kose E, Remer EM, Reynolds JP, Stein R, Rini B, Siperstein A, Berber E. A Modern Assessment of Cancer Risk in Adrenal Incidentalomas: Analysis of 2219 Patients. Ann Surg. 2022 Jan 1;275(1):e238-e244. doi: 10.1097/SLA.0000000000004048. PMID: 32541223.	Univariate analysis
Cyranska-Chyrek E, Szczepanek-Parulska E, Olejarz M, Ruchala M. Malignancy Risk and Hormonal Activity of Adrenal Incidentalomas in a Large Cohort of Patients from a Single Tertiary Reference Center. Int J Environ Res Public Health. 2019 May 27;16(10):1872. doi: 10.3390/ijerph16101872. PMID: 31137898; PMCID: PMC6571894.	Wrong study design

Ohno Y, Sone M, Taura D, Yamasaki T, Kojima K, Honda-Kohmo K, Fukuda Y, Matsuo K, Fujii T, Yasoda A, Ogawa O, Inagaki N. Evaluation of quantitative parameters for distinguishing pheochromocytoma from other adrenal tumors. Hypertens Res. 2018 Mar;41(3):165-175. doi: 10.1038/s41440-017-0002-4. Epub 2018 Jan 18. PMID: 29348428.	Wrong comparison: Pheochromocytomas versus other adrenal tumors
Zekan D, King RS, Hajiran A, Patel A, Deem S, Luchey A. Diagnostic dilemmas: a multi-institutional retrospective analysis of adrenal incidentaloma pathology based on radiographic size. BMC Urol. 2022 Apr 30;22(1):73. doi: 10.1186/s12894-022-01024-5. PMID: 35501776; PMCID: PMC9063092.	Wrong comparison: Radiology versus pathological factors after adrenalectomy
Haan RR, Visser JBR, Pons E, Feelders RA, Kaymak U, Hunink MGM, Visser JJ. Patient-specific workup of adrenal incidentalomas. Eur J Radiol Open. 2017 Sep 7;4:108-114. doi: 10.1016/j.ejro.2017.08.002. PMID: 28932767; PMCID: PMC5596359.	Wrong design: Prediction model for overall factors (not specific diagnostic factors on CT)
Crimì F, Quaia E, Cabrelle G, Zanon C, Pepe A, Regazzo D, Tizianel I, Scaroni C, Ceccato F. Diagnostic Accuracy of CT Texture Analysis in Adrenal Masses: A Systematic Review. Int J Mol Sci. 2022 Jan 7;23(2):637. doi: 10.3390/ijms23020637. PMID: 35054823; PMCID: PMC8776161.	Wrong outcomes
Schloetelburg W, Ebert I, Petritsch B, Weng AM, Dischinger U, Kircher S, Buck AK, Bley TA, Deutschbein T, Fassnacht M. Adrenal wash-out CT: moderate diagnostic value in distinguishing benign from malignant adrenal masses. Eur J Endocrinol. 2021 Dec 10;186(2):183-193. doi: 10.1530/EJE-21-0650. PMID: 34813495; PMCID: PMC8679842.	Univariate analysis
Al-Waeli DK, Mansour AA, Haddad NS. Reliability of adrenal computed tomography in predicting the functionality of adrenal incidentaloma. Niger Postgrad Med J. 2020 Apr-Jun;27(2):101-107. doi: 10.4103/npmj.npmj_156_19. PMID: 32295940.	Wrong study population: Functional adrenal incidentalomas
Clark TJ, Hsu LD, Hippe D, Cowan S, Carnell J, Wang CL. Evaluation of diagnostic accuracy: multidetector CT image noise correction improves specificity of a Gaussian model-based algorithm used for characterization of incidental adrenal nodules. Abdom Radiol (NY). 2019 Mar;44(3):1033-1043. doi: 10.1007/s00261-018-1871-y. PMID: 30600378.	Wrong target condition: Detection of adrenal incidentaloma
Iñiguez-Ariza NM, Kohlenberg JD, Delivanis DA, Hartman RP, Dean DS, Thomas MA, Shah MZ, Herndon J, McKenzie TJ, Arlt W, Young WF Jr, Bancos I. Clinical, Biochemical, and Radiological Characteristics of a Single-Center Retrospective Cohort of 705 Large Adrenal Tumors. Mayo Clin Proc Innov Qual Outcomes. 2017 Dec 21;2(1):30-39. doi:	Wrong study population: Patients with adrenal tumors > 4 centimeters

10.1016/j.mayocpiqo.2017.11.002. PMID: 30225430; PMCID: PMC6124341.	
Hanna FWF, Issa BG, Sim J, Keevil B, Fryer AA. Management of incidental adrenal tumours. BMJ. 2018 Jan 18;360:j5674. doi: 10.1136/bmj.j5674. PMID: 29348269.	Wrong study design
Ahn SH, Kim JH, Baek SH, Kim H, Cho YY, Suh S, Kim BJ, Hong S, Koh JM, Lee SH, Song KH. Characteristics of Adrenal Incidentalomas in a Large, Prospective Computed Tomography-Based Multicenter Study: The COAR Study in Korea. Yonsei Med J. 2018 Jun;59(4):501-510. doi: 10.3349/ymj.2018.59.4.501. PMID: 29749133; PMCID: PMC5949292.	Wrong indextest: HPA axis test and wrong comparison: COAR versus SIE cohort
Helck A, Hummel N, Meinel FG, Johnson T, Nikolaou K, Graser A. Can single-phase dual-energy CT reliably identify adrenal adenomas? Eur Radiol. 2014 Jul;24(7):1636-42. doi: 10.1007/s00330-014-3192-z. Epub 2014 May 8. PMID: 24804633.	Univariate analysis

Literature search strategy

Algemene informatie

Richtlijn: NVVH bijniertumoren	
Uitgangsvraag: Welke kenmerken voorspellen maligniteit bij een gevonden bijnier incidentaloom op een CT-scan?	
Database(s): Ovid/Medline, Embase	Datum: 18-8-2022
Periode: 2010-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: Adrenal incidentalomas AND CT AND (diagostische accuratesse OF prognostisch filter) Omdat in het concept resultaat veel ruis werd aangetroffen over andere incidentaloma's is besloten om specifiek te zoeken naar adrenal incidentaloma's. Alle sleutelartikelen worden gevonden in de basisset. Bij het toepassen van het studiedesign vallen de richtlijnen buiten de gevonden referenties.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 18-8-2022 met relevante zoektermen gezocht vanaf 2010 naar systematische reviews, RCTs en observationele studies over de voorspellende kenmerken bij een gevonden bijnier incidentaloom. De literatuurzoekactie leverde 218 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	35	16	40
RCTs	8	7	9
Observationele studies	131	108	169
Overig			
Totaal			218

Zoekstrategie

Embase

No.	Query	Result
#28	#25 AND #27 3 sleutelartikelen gevonden in de set met studiedesign, richtlijnen worden niet gevonden	3
#27	#14 OR #15 OR #16	291
#26	#9 AND #25 alle sleutelartikelen gevonden in de basisset, zonder studiedesign	6
#25	#19 OR #20 OR #21 OR #22 OR #23 OR #24 sleutelartikelen	6
#24	predicting AND malignancy AND in AND adrenal AND incidentaloma AND evaluation AND of AND a AND novel AND risk AND stratification AND algorithm AND foo AND 2018	1

No.	Query	Result
#23	adrenal AND incidentalomas AND clinical AND controversies AND modified AND recommendations AN D 2016 AND garrett	1
#22	contemporary AND imaging AND of AND incidentally AND discovered AND adrenal AND masses AND w ale AND 2017	1
#21	recommendations AND the AND management AND of AND adrenal AND incidentalomas AND sahdev A ND 2017 AND what AND is AND pertinent AND for AND radiologists	1
#20	clinical AND guidelines AND for AND the AND management AND of AND adrenal AND incidentaloma A ND lee AND 2017 NOT missed:ti	1
#19	acr AND appropriateness AND criteria AND adrenal AND mass AND evaluation AND 2021 AND gupta	1
#18	#16 NOT #15 NOT #14 OBS	131
#17	#15 NOT #14 RCT	8
#16	#9 AND #12	143
#15	#9 AND #11	11
#14	#9 AND #10 SR	35
#13	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* O R subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	13366
#12	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	72006
#11	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR (((non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	19464
#10	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2	73340

No.	Query	Result
	(review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
#9	#8 AND [1-1-2010]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	411
#8	#6 OR #7	789
#7	#3 AND #5	117
#6	#3 AND #4	774
#5	'area under the curve'/exp OR 'brier score'/exp OR 'computer prediction'/exp OR 'c statistic'/exp OR 'c statistics'/exp OR 'integrated discrimination improvement'/exp OR 'net reclassification improvement'/exp OR 'net reclassification index'/exp OR 'prediction'/exp OR 'predictive model'/exp OR 'predictive modeling'/exp OR 'predictive validity'/exp OR 'predictive value'/exp OR 'regression analysis'/exp OR 'statistical model'/exp OR 'area under the curve':ti,ab,kw OR 'brier score*':ti,ab,kw OR 'c statistic*' OR 'computer prediction':ti,ab,kw OR 'decision curve anal*':ti,ab,kw OR (('net reclassification' NEAR/2 (improvement OR index)):ti,ab,kw) OR (((predict* OR statistical*) NEAR/3 (model* OR validity OR value)):ti,ab,kw) OR 'proportional hazards model*':ti,ab,kw OR 'r square*':ti,ab,kw OR regression:ti,ab,kw OR predict*:ti OR multivariate:ti,ab,kw OR multivariab*:ti,ab,kw	30001
#4	'sensitivity and specificity'/de OR sensitiv*:ab,ti OR specific*:ab,ti OR predict*:ab,ti OR 'roc curve':ab,ti OR 'receiver operator':ab,ti OR 'receiver operators':ab,ti OR likelihood:ab,ti OR 'diagnostic error'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'inter observer':ab,ti OR 'intra observer':ab,ti OR interobserver:ab,ti OR intraobserver:ab,ti OR validity:ab,ti OR kappa:ab,ti OR reliability:ab,ti OR reproducibility:ab,ti OR ((test NEAR/2 're-test'):ab,ti) OR ((test NEAR/2 'retest'):ab,ti) OR 'reproducibility'/exp OR accuracy:ab,ti OR 'differential diagnosis'/exp OR 'validation study'/de OR 'measurement precision'/exp OR 'diagnostic value'/exp OR 'reliability'/exp OR 'predictive value'/exp OR ppv:ti,ab,kw OR npv:ti,ab,kw	93287
#3	#1 AND #2	2016
#2	'computer assisted tomography'/exp OR 'cat scan':ti,ab,kw OR ((compute* NEAR/3 tomograph*):ti,ab,kw) OR ct:ti,ab,kw	15782
#1	'adrenal tumor'/exp AND 'incidental finding'/exp OR 'adrenal incidentaloma'/exp OR ((adrenal NEAR/3 incidental*):ti,ab,kw)	3499

Ovid/Medline

#	Searches	Results
18	16 not 15 not 14 OBS	108
17	15 not 14 RCT	7
16	9 and (12 or 13)	122
15	9 and 11	9
14	9 and 10 SR	16
13	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5225241
12	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational	4223215

	adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	
11	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1537965
10	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	611913
9	5 and 8	221
8	6 or 7	8408170
7	Area Under Curve/ or exp Forecasting/ or "Predictive Value of Tests"/ or exp Multivariate Analysis/ or exp Regression Analysis/ or exp Models, Statistical/ or area under the curve.ti,ab,kf. or brier score*.ti,ab,kf. or c statistic*.ti,ab,kf. or computer prediction.ti,ab,kf. or decision curve anal*.ti,ab,kf. or (net reclassification adj2 (improvement or index)).ti,ab,kf. or ((predict* or statistical*) adj3 (model* or validity or value)).ti,ab,kf. or proportional hazards model*.ti,ab,kf. or r square*.ti,ab,kf. or regression.ti,ab,kf. or predict*.ti. or multivaria*.ti,ab,kf.	2271430
6	exp "Sensitivity and Specificity"/ or (Sensitiv* or Specific*).ti,ab. or (predict* or ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab. or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or Diagnosis, Differential/ or Validation Study/	7489883
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	502
4	limit 3 to yr="2010 -Current"	532
3	1 and 2	993
2	exp Tomography, X-Ray Computed/ or computed tomograph*.ti,ab,kf. or ct.ti,ab,kf. or cts.ti,ab,kf. or cat scan*.ti,ab,kf. or computer assisted tomograph*.ti,ab,kf. or computerized tomograph*.ti,ab,kf. or computerised tomograph*.ti,ab,kf. or computed x ray tomograph*.ti,ab,kf. or computed xray tomograph*.ti,ab,kf.	805606
1	(Adrenal Gland Neoplasms/ and exp Incidental Findings/) or (incidental* adj3 adrenal).ti,ab,kf.	2126

Module 2 – Diagnostiek morbus Conn

Uitgangsvraag
Welke diagnostische test is het meest effectief om de locatie van aldosteron overproductie vast te stellen bij patiënten met morbus Conn (primair hyperaldosteronisme)?

Introductie
Primair hyperaldosteronisme (PHA) is een belangrijke oorzaak van secundaire hypertensie en is de oorzaak van 5-15% van de totale hypertensie populatie. Vroegtijdige diagnose en behandeling zijn belangrijk omdat patiënten een hogere cardiovasculaire morbiditeit en mortaliteit hebben. In de meeste gevallen wordt PHA veroorzaakt door een unilateraal aldosteronproducerend adenoom of door bilaterale hyperplasie en daarom is een goed onderscheid tussen de twee van cruciaal belang. De eerste wordt namelijk behandeld met adrenalectomie en de laatste met medicatie zoals mineralocorticoïdreceptorantagonisten. Op dit moment wordt de locatie van het PHA veelal vastgesteld met behulp van veneuze bijniervene sampling (AVS). Deze modaliteit wordt ingezet ter differentiatie van de aangedane zijde van de bijnier die leidt tot aldosteron overproductie. In het verleden gebeurde dit middels een CT scan of andere beeldvormende modaliteiten. AVS is invasief onderzoek, kostbaar en vereist specifieke expertise waardoor het beperkt beschikbaar is. Ondanks deze nadelen wordt AVS als de diagnostische standaard beschouwd in de ESE richtlijn (Fassnacht, 2016). De vraag is of CT beter geschikt is als diagnostische modaliteit ter differentiatie van de aangedane zijde van de bijnier.

Search and select
A systematic review of the literature was performed to answer the following question: What are the outcomes of localizing the affected adrenal gland with CT-scan compared with Adrenal Vein Sampling in patients with primary aldosteronism (m. Conn)?

P (Patients)	Patients with primary aldosteronism (m. Conn), diagnosed biochemically with a sodium chloride perfusion test
I (Intervention)	CT-scan
C (Control)	Adrenal Vein Sampling (AVS)
R (Reference)	Pathology
O (Outcomes)	Blood pressure control, normokalaemia, complications, costs and diagnostic accuracy
T (Target condition)	Localization of affected adrenal gland

<u>Relevant outcome measures</u>
The guideline development group considered blood pressure regulation and normokalaemia as *critical* outcome measures for decision making and complications, costs and diagnostic accuracy (specificity) as *important* outcome measures for decision making.

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

The working group defined the following differences as minimally clinically (patient) important:

- Blood pressure: ≥10mmHg difference in target blood pressure
- Normokalaemia: ≥5% (difference) in establishing normokalaemia

- Complications: Absolute difference >5% for lethal complications, or >25% for serious complications
- Costs: >10%
- Diagnostic accuracy: No differences reported

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 17-10-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 364 hits. Studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICO;
- The intervention and comparison had to be as defined in the PICO;
- One or more reported outcomes had to be as defined in the PICO;
- Research type: Systematic review, randomized-controlled trial regarding clinical outcomes and observational studies regarding diagnostic accuracy;
- Articles written in English or Dutch

Twenty 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 one study was included.

Results
One study 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
Dekkers (2016) performed a randomised diagnostic trial: The Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography Scan (SPARTACUS) trial. Patients were randomly assigned to diagnosis for localization of affected adrenal gland by Computed Tomography Scan (CT-scan) or Adrenal Vein Sampling (AVS). Patients with hypertension needing three or more antihypertensive drugs in adequate doses or hypertension accompanied by spontaneous or diuretic-induced hypokalemia and with confirmation of primary aldosteronism by an oral or intravenous salt-loading test, were included. Patients refusing to undergo AVS, CT or adrenalectomy or with suspicion of glucocorticoid-remediable aldosteronism or adrenocortical carcinoma, severe comorbidity potentially interfering with treatment or health-related quality of life, or requirement of medication interfering with the study protocol were excluded. In total, 196 patients were included. 99 patients were randomly assigned to diagnosis with an adrenal CT-scan. In case of unilaterally enlarged adrenal with a normal contralateral gland (unilateral disease), patients were treated by adrenalectomy. In case of bilaterally enlarged or normal adrenal glands (bilateral disease), patients were treated with mineralocorticoid receptor antagonist (MRA). 97 patients were assigned to diagnosis by AVS. Unilateral disease was diagnosed when the lateralisation index was 4.0 or higher and the suppression index was less than or equal to 1.0. Patients with unilateral disease were treated by adrenalectomy. Patients without unilateral disease were treated with MRA.
Mean age in the CT-group and the AVS-group was 53.1 years. In the CT-group, 75 percent was male. In the AVS-group, 82 percent was male. Mean Body Mass Index (BMI) in the CT-group was 28.4 kg/m^2 and in the AVS-group 29.5 kg/m^2. There were no significant differences between treatment groups at baseline.

Dekkers (2016) reported blood pressure control, potassium levels (normokalaemia), complications and costs. All reported outcomes were at one-year follow-up.

Results

Blood pressure control

Dekkers (2016) reported median 24-hour ambulatory systolic blood pressure of 127 mm Hg (IQR 120-138) in the CT-group and 128 mm Hg (IQR 121-135) in the AVS-group.

Dekkers (2016) also reported median 24-hour ambulatory diastolic blood pressure. In the CT-group median diastolic pressure was 80 mm Hg (IQR 75-86) and in the AVS-group 81 mm Hg (IQR 76-85).

Normokalaemia

Dekkers (2016) reported potassium levels in both groups. In the CT-group the median potassium level was 4.3 mmol/L (IQR 4.0-4.6). In the AVS-group the median potassium level was 4.2 mmol/L (IQR 4.0-4.6).

Complications

Dekkers (2016) reported Adverse Events (AE's) and Serious Adverse Events (SAE's). In the CT-group 150 AE's (41%) were reported and in the AVS-group 175 AE's (48%).
In the CT-group nine SAE's (2%) were reported and in the AVS-group 12 SAE's (3%).

Costs

Dekkers (2016) reported total costs for diagnosis with CT-scan and AVS. Median total costs in the CT-group were €4227.85 (IQR 3604.2-4851.5) and in the AVS-group €6746.27 (IQR 5965.3-7527.2) resulting in a mean difference of €2285.51 (IQR 1322.75-3248.26).

Diagnostic accuracy

The included study did not report diagnostic accuracy.

Level of evidence of the literature

Blood pressure control

The level of evidence regarding the outcome measure *blood pressure control* was downgraded by two levels because of study limitations (-1; risk of bias regarding allocation concealment and blinding) and number of included patients (-1; imprecision because of single study and small sample size). The evidence is therefore graded as low.

Normokalaemia

The level of evidence regarding the outcome measure *normokalaemia* was downgraded by three levels because of study limitations (-1; risk of bias regarding allocation concealment and blinding) and number of included patients (-1; imprecision because of single study and small sample size). The evidence is therefore graded as low.

Complications

The level of evidence regarding the outcome measure *complications* was downgraded by two levels because of study limitations (-1; risk of bias regarding allocation concealment and blinding) and number of included patients (-1; imprecision because of single study and small sample size). The evidence is therefore graded as low.

Costs
The level of evidence regarding the outcome measure *costs* was downgraded by two levels because of study limitations (-1; risk of bias regarding allocation concealment and blinding) and number of included patients (-1; imprecision because of single study and small sample size). The evidence is therefore graded as low.

Conclusions

Low GRADE	The evidence suggests that detection of location of affected adrenal gland by CT-scan results in little to no difference in **blood pressure control** when compared with AVS in patients with patients with primary aldosteronism (m. Conn). *Source: Dekkers, 2016*

Low GRADE	The evidence suggests that detection of location of the affected adrenal gland by CT-scan results in little to no difference regarding **normokalaemia** when compared with AVS in patients with primary aldosteronism (m. Conn). *Source: Dekkers, 2016*

Low GRADE	The evidence suggests that detection of location of affected adrenal gland by CT-scan results in little to no difference in **complications** when compared with AVS in patients with patients with primary aldosteronism (m. Conn). *Source: Dekkers, 2016*

Low GRADE	The evidence suggests that detection of location of the affected adrenal gland by CT-scan results in a reduction of **costs** when compared with AVS in patients with primary aldosteronism (m. Conn). *Source: Dekkers, 2016*

No GRADE	No evidence was found regarding the comparison of CT-scan and AVS regarding **diagnostic accuracy** for detecting the affected adrenal gland in patients with primary aldosteronism (m. Conn). *Source: -*

Overwegingen – van bewijs naar aanbeveling
Voor- en nadelen van de interventie en de kwaliteit van het bewijs
In de samenvatting is een gerandomiseerde diagnostische trial geïncludeerd (Dekkers, 2016) en zijn er voor de cruciale uitkomstmaten (bloeddruk controle en normokalemie) uitkomsten gerapporteerd. De uitkomst bloeddrukcontrole is gerapporteerd als 24-uurs systolische en diastolische bloeddruk, waarbij geen klinisch relevant verschil tussen detectie van de aangedane bijnier met een CT-scan of AVS, gevonden is. Met betrekking tot de uitkomstmaat normokalemie is er geen klinisch relevant verschil gevonden tussen beide groepen.
Voor de belangrijke uitkomstmaten, complicaties en kosten, zijn door de studie van Dekkers (2016) ook uitkomsten gerapporteerd. Er is geen klinisch relevant verschil gevonden tussen detectie met de CT-scan of AVS betreffende complicaties maar wel met betrekking tot kosten waarbij de kosten van de CT-scan lager waren dan die van detectie middels AVS. Er zijn geen studies geïncludeerd die hebben gekeken naar diagnostische accuratesse.

Alle uitkomstmaten, zowel cruciaal als belangrijk, hadden een lage bewijskracht waarbij de uitkomst normokalemie zelfs zeer laag was. Reden voor de lage bewijskracht was het mogelijke risico op bias door ontbreken van blindering en de enkele studie met relatief kleine studie populatie.

Primair hyperaldosteronisme (PHA) is de meest frequente oorzaak van secundaire hypertensie, waarbij recente studies laten zien dat de prevalentie hoger is dan voorheen werd aangenomen. De kans op cardiovasculaire morbiditeit is hoger bij patiënten met PHA vergeleken met patiënten met essentiële hypertensie, ondanks vergelijkbare bloeddrukregulatie. Het is daarom van belang PHA vroegtijdig op te sporen bij patiënten met hypertensie teneinde een gerichte en indien mogelijk curatieve behandeling te geven.
De meest recente richtlijn met betrekking tot diagnostiek en behandeling van PHA is geschreven vanuit de Endocrine Society en dateert uit 2016, met een aanvullende revisie gepubliceerd in 2018 (Fassnacht, 2016; Fassnacht, 2018). Enkele kernpunten worden hieronder beschreven.

Wie screenen voor PHA?
Bij de volgende patiëntengroepen wordt aanbevolen om te screenen op PHA:

- Patiënten met persisterend verhoogde bloeddrukwaarden van > 150/100 mmHg bij 3 metingen op verschillende dagen
- Patiënten met verhoogde bloeddruk (>140/90 mmHg) onder 3 antihypertensiva
- Patiënten met gecontroleerde bloeddruk (<140/90 mmHg) onder 4 antihypertensiva
- Patiënten met hypertensie en spontane of diuretica-geïnduceerde hypokaliaemie
- Patiënten met hypertensie en een bijnierincidentaloom
- Patiënten met hypertensie en een slaap-apnoe syndroom
- Patiënten met hypertensie en een familie anamnese van early-onset hypertensie en/of CVA op jonge leeftijd (< 40 jaar)
- Eerstegraads familieleden met hypertensie van patiënten met PHA

Hoe screenen voor PHA?
Aanbevolen wordt om te screenen voor PHA met de plasma aldosteron/renine ratio.
Aandachtspunten plasma aldosteron/renine ratio:

- Afname ’s ochtends 2 uur na ontwaken en na 5-15 minuten zittende positie
- Afname bij voorkeur onder neutrale medicatie
- Afname bij normale kalium concentraties
- Cut-off waarde is afhankelijk van de gebruikte laboratoriummethoden

Bij een verhoogde aldosteron/renine ratio wordt aanbevolen de diagnose PHA te bevestigen met een confirmatietest. Bij patiënten met spontane hypokaliaemie, niet-detecteerbare renine waarden en aldosteron waarden > 550 pmol/l kan worden overwogen de confirmatietest achterwege te laten. Wereldwijd worden verschillende confirmatietesten gebruikt: de orale zoutbelastingtest, de intraveneuze zoutbelastingtest, de fludrocortison suppressietest en de captopril test. In Nederland wordt vooral de intraveneuze zoutbelastingtest gebruikt.

Aandachtspunten intraveneuze zoutbelastingtest:

- Afname bij voorkeur onder neutrale medicatie
- Afname bij normale kalium concentraties

- Interpretatie: na zoutinfusie duiden aldosteron waarden >280 pmol/l op aanwezigheid van PHA en maken aldosteron waarden <140 pmol/l PH onwaarschijnlijk. Er blijft echter een grijs gebied met aldosteron waarden tussen 140 en 280 pmol/l waarbij de diagnose onzeker is.

Voor verdere details omtrent methodologie en interpretatie van screening- en confirmatietests voor PHA wordt verwezen naar de Endocrine Society richtlijntekst (Funder, 2016).

Subtype classificatie

Na de biochemische diagnose PHA wordt in de European Society of Endocrinology (ESE) richtlijn aanbevolen om bij iedere patiënt CT onderzoek te verrichten om grote bijnierlaesies als gevolg van een bijniercarcinoom uit te sluiten en ter voorbereiding op aanvullend onderzoek middels bijniervenesampling en eventuele operatie (Fassnacht, 2016).
Oorzaken van PHA zijn een unilateraal bijnieradenoom, bilaterale micro- of macroadenomen, uni- of bilaterale idiopatische bijnierhyperplasie en unilateraal bijniercarcinoom.
In de huidige praktijk worden de resultaten van CT onderzoek en bijniervenesampling gebruikt om de bron van PHA te lokaliseren en tot een therapiebesluit te komen.
Uitkomsten van CT onderzoek kunnen zijn:

- Normale bijnieren
- Minimale unilaterale bijnierverdikking
- Unilateraal microadenoom (<1cm)
- Bilaterale micro- en/of macroadenomen
- Unilateraal carcinoom (>4cm)

Imaging van de bijnieren met CT heeft echter beperkingen. Idiopathische uni- of bilaterale bijnierhyperplasie kan gepaard gaan met een normaal CT beeld of als minimale micronodulaire verandering. Kleine aldosteron-producerende adenomen zouden ook ten onrechte als hyperplasie afgegeven kunnen worden. Andersom kunnen duidelijke microadenomen gebieden van hyperplasie representeren of een niet-functionele nodulaire verandering. Verder komen niet-functionele unilaterale bijnieradenomen frequent voor, zeker met stijgende leeftijd (>35 jaar) en deze zijn middels CT niet te onderscheiden van aldosteron-producerende bijnieradenomen. Bij de geschetste situaties is het duidelijk dat op grond van alleen CT onderzoek ten onrechte een unilaterale adrenalectomie uitgevoerd zou kunnen worden. Dit wordt onderstreept door de concordantie van slechts 54% tussen bevindingen bij CT en bijniervene-sampling met betrekking tot lateralisatie van de oorzaak van PHA.
Lateralisatie bij PHA is leidend is voor subtypering van de oorzaak en mogelijke behandeling. Immers bij unilaterale ziekte (adenoom of hyperplasie) resulteert adrenalectomie in normokaliemie en genezing of verbetering van hypertensie terwijl bij bilaterale ziekte gerichte medicamenteuze behandeling met een MRA het meest effectief is. Bijniervenesampling heeft een hoge sensitiviteit (95%) en specificiteit (100%) voor de detectie van unilateraal aldosteron overproductie en lijkt superieur ten opzichte van CT (voor details omtrent methodologie en interpretatie van de bijniervene-sampling wordt verwezen naar de Endocrine Society richtlijntekst[1]). Derhalve beveelt de Endocrine Society richtlijn bijniervenesampling aan voor subtype classificatie van iedere PHA patiënt die een potentiële kandidaat is voor adrenalectomie (en die dit ook wenselijk vindt) teneinde een onnodige bijnierresectie op grond van CT onderzoek te voorkomen. Een uitzondering kan gemaakt worden voor jonge patiënten (<35 jaar) met evident PHA en een solitaire bijnierlaesie op CT scan.
Dit is een rationele strategie, echter de publicatie van de SPARTACUS studie laat hier wel een ander licht op schijnen (Dekkers, 2016). In deze studie werden PHA patiënten gerandomiseerd

voor besluitvorming tot adrenalectomie of medicamenteuze behandeling (met een MRA) op basis van CT of op basis van bijniervenesampling. Eén jaar na start van de behandeling bleken de uitkomsten in beide groepen gelijk voor wat betreft bloeddrukregulatie (bloeddruk waarden en intensiteit van antihypertensieve behandeling), biochemische remissie en kwaliteit van leven. Deze studie heeft veel stof doen opwaaien in de internationale hypertensiewereld zoals beschreven in een commentaar door Williams en Reincke (2018). Tot op heden is SPARTACUS de enige gerandomiseerde uitkomstgerichte prospectieve studie, die de standaard toepassing van AVS voor subtypering van PHA ter discussie heeft weten te stellen.
De SPARTACUS studie is tot op heden niet gerepliceerd en daarom is vooralsnog het advies om de Endocrine Society guideline in principe te volgen. Een punt van discussie is wel de leeftijdsgrens (35 jaar) waarboven nu geadviseerd wordt om bij een éénzijdig adenoom een bijniervenesampling te verrichten. De leeftijdsrange 35-50 jaar is een grijs gebied en aanvullend onderzoek is nodig ter ondersteuning van de leeftijdsgrens van 35 jaar om over te gaan op een bijniervenesampling.

Genetisch onderzoek
Voor patiënten met PHA die jonger zijn dan 20 jaar en patiënten met een familie geschiedenis van PHA of een CVA op jonge leeftijd (<40 jaar) wordt genetische screening geadviseerd op familiair hyperaldosteronisme type I (glucocorticoid remediable aldosteronism). Bij zeer jonge patiënten met PHA kan genetische screening op germline mutaties zoals bijvoorbeeld het KCNJ5 gen (familiair hyperaldosteronisme type I) worden overwogen.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Het is belangrijk om de voor- en nadelen van CT en AVS met de patiënt te bespreken. Samen beslissen heeft hierbij een rol, bijvoorbeeld in geval van angst voor CT of AVS.

Kosten (middelenbeslag)
De kosten zijn significant hoger voor diagnostiek met AVS en worden grotendeels veroorzaakt door de noodzaak van klinische observatie (dagopname) na (invasieve) AVS.

Aanvaardbaarheid, haalbaarheid en implementatie
AVS kent beperkingen voor implementatie waardoor slechts enkele ziekenhuizen in Nederland AVS aanbieden. AVS is een technische complexe procedure die invasief is en belastend voor de patiënt en veel ervaring vereist van de radioloog. Ondanks de beperkte beschikbaarheid in Nederland is het wel aan te bevelen. Dit geeft een reden voor verder onderzoek naar een beter beschikbare, goedkopere, niet-invasieve manier van diagnostiek (zoals bijvoorbeeld de Pentixafor PET-CT (Chaman Baz, 2022).

Aanbeveling
Rationale van de aanbeveling: weging van argumenten voor en tegen de diagnostische procedure
In de ESE richtlijn wordt vooralsnog AVS aanbevolen voor subtypering bij iedere patiënt met primair hyperaldosteronisme die potentiele kandidaat is voor adrenalectomie (Fassnacht, 2016).
Alleen bij patiënten met evident primair hyperaldosteronisme <35 jaar kan een uitzondering worden gemaakt bij een solitaire bijnierlaesie op CT scan.
Het enige gerandomiseerde uitkomstgerichte prospectieve onderzoek naar de diagnostische waarde van AVS versus CT heeft niet geleid tot verandering van de richtlijn en is nog niet gerepliceerd.

Shared decision making dient plaats te vinden in gesprek met de patiënt ten aanzien van de voor- en nadelen van de verschillende diagnostische methoden.

Overweeg Adrenal Vein Sampling (AVS) voor subtypering van primair hyperaldosteronisme en de beslissing tot adrenalectomie.

Verricht een CT-scan bij jonge patiënten <35 jaar voor subtypering van primair hyperaldosteronisme en de beslissing tot adrenalectomie.

Bespreek met de patiënt de voor- en nadelen van AVS en CT. Hierbij dienen de volgende zaken ten minste besproken te worden:

- Nadelen AVS: Klinische opname noodzakelijk, invasief en technisch complex, beperkte beschikbaarheid
- Voordelen AVS: Diagnostiek conform de richtlijn en enige mogelijkheid van functionele diagnostiek

Literatuur

Chaman Baz AH, van de Wiel E, Groenewoud H, Arntz M, Gotthardt M, Deinum J, Langenhuijsen J. CXCR4-directed [^{68}Ga]Ga-PentixaFor PET/CT versus adrenal vein sampling performance: a study protocol for a randomised two-step controlled diagnoStic Trial Ultimately comparing hypertenSion outcome in primary aldosteronism (CASTUS). BMJ Open. 2022 Aug 23;12(8):e060779. doi: 10.1136/bmjopen-2022-060779. PMID: 35998969; PMCID: PMC9403157.

Dekkers T, Prejbisz A, Kool LJS, Groenewoud HJMM, Velema M, Spiering W, Kołodziejczyk-Kruk S, Arntz M, Kądziela J, Langenhuijsen JF, Kerstens MN, van den Meiracker AH, van den Born BJ, Sweep FCGJ, Hermus ARMM, Januszewicz A, Ligthart-Naber AF, Makai P, van der Wilt GJ, Lenders JWM, Deinum J; SPARTACUS Investigators. Adrenal vein sampling versus CT scan to determine treatment in primary aldosteronism: an outcome-based randomised diagnostic trial. Lancet Diabetes Endocrinol. 2016 Sep;4(9):739-746. doi: 10.1016/S2213-8587(16)30100-0. Epub 2016 Jun 17. PMID: 27325147.

Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016 Aug;175(2):G1-G34. doi: 10.1530/EJE-16-0467. PMID: 27390021.

Fassnacht M, Dekkers OM, Else T, Baudin E, Berruti A, de Krijger R, Haak HR, Mihai R, Assie G, Terzolo M. European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2018 Oct 1;179(4):G1-G46. doi: 10.1530/EJE-18-0608. PMID: 30299884.

Funder JW et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016 May;101(5):1889-916.

Williams TA & Reincke M. MANAGEMENT OF ENDOCRINE DISEASE: Diagnosis and management of primary aldosteronism: the Endocrine Society guideline 2016 revisited. Eur J Endocrinol 2018 Jul;179(1):R19-R29.

Bijlagen bij module Diagnostiek morbus Conn

Evidencetabellen

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

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Dekkers, 2016	Type of study: Randomised Controlled Trial (RCT) Setting and country: Multicenter study, Netherlands and Poland Funding and conflicts of interest: Funder of the study (Netherlands Organisation for Health Research and Development-Medical Sciences) had no role in the study design, data collection, data analysis, data	Inclusion criteria: - Age 18 years or older - Hypertension needing three or more antihypertensive drugs in adequate doses or hypertension accompanied by spontaneous or diuretic-induced hypokalemia - Confirmation of primary aldosteronism by an oral or intravenous salt-loading test Exclusion criteria: - Refusing to undergo AVS, CT or adrenalectomy - Pregnancy - Suspicion of glucocorticoid-	Intervention test: Adrenal CT-scan, performed in all medical centers assessed by a local radiologist and centrally revised in Nijmegen. In case of unilaterally enlarged adrenal with a normal contralateral gland (unilateral disease), patients were treated by adrenalectomy. In case of bilaterally enlarged or normal adrenal glands (bilateral disease), patients were treated with MRA.	Control test: Adrenal Vein Sampling (AVS) procedure at Radboud University Medical Center, University Medical Center Groningen (both Netherlands) and Institute of Cardiology in Warsaw (Poland). AVS was performed under continuous cosyntropin stimulation with sequential catheterisation of adrenal veins. Successful cannulation was defined as a selectivity index of 3.0 or higher. Unilateral disease was diagnosed when the lateralisation index was 4.0 or higher and the suppression index was less than or equal to 1.0. Patients with unilateral disease were treated by adrenalectomy.	Length of follow-up: One year Loss-to-follow-up: Intervention: N=7 (7%) Reasons: - N=3: Lost to follow-up before CT-scan or treatment - N=4: Discontinued follow-up from treatment with MRA (N=1) or adrenalectomy (N=3) Control: N=5 (5%) Reasons: - N=1: Withdrew consent before AVS - N=4 Discontinued follow-up from treatment with adrenalectomy	Outcome measures and effect size (include 95%CI and p-value if available): Blood pressure control Median 24h ambulatory systolic blood pressure in mm Hg (IQR) I: 127 (120-138) C: 128 (121-135) Median 24h ambulatory diastolic blood pressure in mm Hg (IQR) I: 80 (75-86) C: 81 (76-85) Normokalaemia Median Potassium in mmol/L (IQR) I: 4.3 (4.0-4.6) C: 4.2 (4.0-4.6) Complications Adverse events I: N=150 (41%) C: N=175 (48%)	Authors conclusion: In conclusion, treatment of primary aldosteronism on the basis of CT or AVS did not show significant differences in clinical benefits for patients after 1 year of follow-up. No diagnostic accuracy outcomes because of lack of reference standard.

	interpretation or writing of the report. Authors declare no competing interests.	remediable aldosteronism - Suspicion of adrenocortical carcinoma - Severe comorbidity potentially interfering with treatment or health-related quality of life - Requirement of medication interfering with the study protocol <u>N total at baseline</u>: Intervention: 99 Control: 97 <u>Important prognostic factors</u>[2]: *Mean age in years (SD):* *I: 53.1 (9.4)* *C: 53.1 (9.7)* *Sex:* *I: 75% M* *C: 82% M* *Mean BMI in kg/m² (SD):* *I: 28.4 (4.1)* *C: 29.5 (4.7)* *Median 24h ambulatory systolic blood*		Patients without unilateral disease were treated with a mineralocorticoid receptor antagonist (MRA). During follow-up of adrenalectomy, antihypertensive medication was initiated and adjusted to achieve a target blood pressure of less than 135/85 mm Hg using semiautomatic device or less than 140/90 mm Hg using office measurement of blood pressure. In case of treatment with MRA antagonists, patients started on 25 mg of spironolactone if necessary to be increased to a maximum dose of two times 100 mg daily. In case of side-effects to spironolactone, eplerenone was prescribed to a maximum of two times 200 mg daily.		Serious adverse events I: N=9 (2%) C: N=12 (3%) <u>Costs</u> Mean costs (IQR) I: €4227.85 (3604.2-4851.5) C: €6746.27 (5965.3-7527.2) MD: €2285.51 (95%CI 1322.75-3248.26)	

		pressure in mm Hg (IQR): *I: 143 (129-155)* *C: 148 (133-161)* *Median 24h ambulatory diastolic blood pressure in mm Hg (IQR):* *I: 89 (82-98)* *C: 89 (84-98)* *Median serum sodium in mmol/L (IQR):* *I: 142 (140-143)* *C: 142 (140-143)* *Adrenalectomy procedure:* *I: N=49 (49%)* *C: N=50 (51%)* *MRA therapy:* *I: N=47 (47%)* *C: N=46 (47%)* Groups were comparable at baseline					

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

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Dekkers, 2016	Definitely yes; Reason: Randomisation using a web-based algorithm stratified by study centre and minimised for sex, age, blood pressure and intensity of antihypertensive medication.	Definitely no; Reason: Patients, investigators and statisticians were not masked to treatment allocation.	Definitely no; Reason: Patients, investigators and statisticians were not masked blinded.	Probably yes; Reason: Loss to follow-up was infrequent in intervention and control group.	Definitely yes; Reason: All relevant outcomes were reported.	Definitely yes; Reason: No other problems noted	**Some concerns regarding allocation concealment and blinding**

Table of excluded studies

Reference	Reason for exclusion
Yan Y, Sun HW, Qi Y. Prognosis of adrenalectomy guided by computed tomography versus adrenal vein sampling in patients with primary aldosteronism: A systematic review and meta-analysis. J Clin Hypertens (Greenwich). 2022 Feb;24(2):106-115. doi: 10.1111/jch.14395. Epub 2022 Jan 22. PMID: 35064745; PMCID: PMC8845452.	Wrong study population
Zhou Y, Wang D, Jiang L, Ran F, Chen S, Zhou P, Wang P. Diagnostic accuracy of adrenal imaging for subtype diagnosis in primary aldosteronism: systematic review and meta-analysis. BMJ Open. 2020 Dec 31;10(12):e038489. doi: 10.1136/bmjopen-2020-038489. PMID: 33384386; PMCID: PMC7780716.	Wrong index test
Kempers MJ, Lenders JW, van Outheusden L, van der Wilt GJ, Schultze Kool LJ, Hermus AR, Deinum J. Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. Ann Intern Med. 2009 Sep 1;151(5):329-37. doi: 10.7326/0003-4819-151-5-200909010-00007. PMID: 19721021.	Wrong index test
Chen C, Yunfeng HE, Zhang Y, Wu X, Pu J. To compare the role on determining the functional location of primary hyperaldosteronism by multi-slice spiral CT and by adrenal vein sampling. Chinese Journal of Urology. 2019. 12; 385-388	Wrong language
Williams TA, Burrello J, Sechi LA, Fardella CE, Matrozova J, Adolf C, Baudrand R, Bernardi S, Beuschlein F, Catena C, Doumas M, Fallo F, Giacchetti G, Heinrich DA, Saint-Hilary G, Jansen PM, Januszewicz A, Kocjan T, Nishikawa T, Quinkler M, Satoh F, Umakoshi H, Widimský J Jr, Hahner S, Douma S, Stowasser M, Mulatero P, Reincke M. Computed Tomography and Adrenal Venous Sampling in the Diagnosis of Unilateral Primary Aldosteronism. Hypertension. 2018 Sep;72(3):641-649. doi: 10.1161/HYPERTENSIONAHA.118.11382. PMID: 29987100.	Wrong design
Raman SP, Lessne M, Kawamoto S, Chen Y, Salvatori R, Prescott JD, Fishman EK. Diagnostic performance of multidetector computed tomography in distinguishing unilateral from bilateral abnormalities in primary hyperaldosteronism: comparison of multidetector computed tomography with adrenal vein sampling. J Comput Assist Tomogr. 2015 May-Jun;39(3):414-8. doi: 10.1097/RCT.0000000000000208. PMID: 25594382.	Wrong outcome; No reference test
Lim V, Guo Q, Grant CS, Thompson GB, Richards ML, Farley DR, Young WF Jr. Accuracy of adrenal imaging and adrenal venous sampling in predicting surgical	Wrong study population

cure of primary aldosteronism. J Clin Endocrinol Metab. 2014 Aug;99(8):2712-9. doi: 10.1210/jc.2013-4146. Epub 2014 May 5. PMID: 24796926.	
Lee SH, Kim JW, Yoon HK, Koh JM, Shin CS, Kim SW, Kim JH. Diagnostic Accuracy of Computed Tomography in Predicting Primary Aldosteronism Subtype According to Age. Endocrinol Metab (Seoul). 2021 Apr;36(2):401-412. doi: 10.3803/EnM.2020.901. Epub 2021 Mar 31. PMID: 33789036; PMCID: PMC8090455.	Wrong outcome
Umakoshi H, Ogasawara T, Takeda Y, Kurihara I, Itoh H, Katabami T, Ichijo T, Wada N, Shibayama Y, Yoshimoto T, Ogawa Y, Kawashima J, Sone M, Inagaki N, Takahashi K, Watanabe M, Matsuda Y, Kobayashi H, Shibata H, Kamemura K, Otsuki M, Fujii Y, Yamamto K, Ogo A, Yanase T, Okamura S, Miyauchi S, Suzuki T, Tsuiki M, Naruse M. Accuracy of adrenal computed tomography in predicting the unilateral subtype in young patients with hypokalaemia and elevation of aldosterone in primary aldosteronism. Clin Endocrinol (Oxf). 2018 May;88(5):645-651. doi: 10.1111/cen.13582. Epub 2018 Mar 13. PMID: 29464741.	Wrong outcome; No reference test
Ladurner R, Sommerey S, Buechner S, Dietz A, Degenhart C, Hallfeldt K, Gallwas J. Accuracy of adrenal imaging and adrenal venous sampling in diagnosing unilateral primary aldosteronism. Eur J Clin Invest. 2017 May;47(5):372-377. doi: 10.1111/eci.12746. Epub 2017 Apr 7. PMID: 28299775.	No comparison
Kamemura K, Wada N, Ichijo T, Matsuda Y, Fujii Y, Kai T, Fukuoka T, Sakamoto R, Ogo A, Suzuki T, Umakoshi H, Tsuiki M, Naruse M. Significance of adrenal computed tomography in predicting laterality and indicating adrenal vein sampling in primary aldosteronism. J Hum Hypertens. 2017 Mar;31(3):195-199. doi: 10.1038/jhh.2016.61. Epub 2016 Sep 1. PMID: 27582025.	Wrong outcomes
Zhu L, Zhang Y, Zhang H, Zhou W, Shen Z, Zheng F, Tang X, Tao B, Zhang J, Lu X, Xu J, Chu S, Zhu D, Gao P, Wang JG. Comparison between adrenal venous sampling and computed tomography in the diagnosis of primary aldosteronism and in the guidance of adrenalectomy. Medicine (Baltimore). 2016 Sep;95(39):e4986. doi: 10.1097/MD.0000000000004986. PMID: 27684853; PMCID: PMC5265946.	Wrong outcome
Kim JY, Kim SH, Lee HJ, Kim YH, Kim MJ, Cho SH. Adrenal venous sampling for stratifying patients for surgery of adrenal nodules detected using dynamic contrast enhanced CT. Diagn Interv Radiol. 2014 Jan-	Wrong study population

Feb;20(1):65-71. doi: 10.5152/dir.2013.13144. PMID: 24047720; PMCID: PMC4463251.	
Zhao JS, Li Y, He M, Liu Q, Shang MY, Wang HB. [Value of adrenal venous sampling in the subtype diagnosis of primary aldosteronism]. Zhonghua Yi Xue Za Zhi. 2013 Feb 26;93(8):579-82. Chinese. PMID: 23663335.	Wrong language (Chinese article)
Graham UM, Ellis PK, Hunter SJ, Leslie H, Mullan KR, Atkinson AB. 100 cases of primary aldosteronism: careful choice of patients for surgery using adrenal venous sampling and CT imaging results in excellent blood pressure and potassium outcomes. Clin Endocrinol (Oxf). 2012 Jan;76(1):26-32. doi: 10.1111/j.1365-2265.2011.04177.x. PMID: 21767289.	Wrong outcomes
Sarlon-Bartoli G, Michel N, Taieb D, Mancini J, Gonthier C, Silhol F, Muller C, Bartoli JM, Sebag F, Henry JF, Deharo JC, Vaisse B. Adrenal venous sampling is crucial before an adrenalectomy whatever the adrenal-nodule size on computed tomography. J Hypertens. 2011 Jun;29(6):1196-202. doi: 10.1097/HJH.0b013e32834666af. PMID: 21478754.	Wrong comparison
Zarnegar R, Bloom AI, Lee J, Kerlan RK Jr, Wilson MW, Laberge JM, Gordon RL, Kebebew E, Clark OH, Duh QY. Is adrenal venous sampling necessary in all patients with hyperaldosteronism before adrenalectomy? J Vasc Interv Radiol. 2008 Jan;19(1):66-71. doi: 10.1016/j.jvir.2007.08.022. PMID: 18192469.	Wrong comparison
Mulatero P, Bertello C, Rossato D, Mengozzi G, Milan A, Garrone C, Giraudo G, Passarino G, Garabello D, Verhovez A, Rabbia F, Veglio F. Roles of clinical criteria, computed tomography scan, and adrenal vein sampling in differential diagnosis of primary aldosteronism subtypes. J Clin Endocrinol Metab. 2008 Apr;93(4):1366-71. doi: 10.1210/jc.2007-2055. Epub 2008 Jan 15. PMID: 18198224.	No comparison
Minami I, Yoshimoto T, Hirono Y, Izumiyama H, Doi M, Hirata Y. Diagnostic accuracy of adrenal venous sampling in comparison with other parameters in primary aldosteronism. Endocr J. 2008 Oct;55(5):839-46. doi: 10.1507/endocrj.k07e-164. Epub 2008 May 23. PMID: 18497447.	Wrong outcomes

Zoekverantwoording

Algemene informatie

Richtlijn: NVvH Bijniertumoren	
Uitgangsvraag: UV 01 Welke diagnostische test kan het beste gebruikt worden om de locatie van aldosteron overproduktie vast te stellen bij patiënten met m. Conn?	
Database(s): Ovid/Medline, Embase	Datum:17-10-2022
Periode: 2002-	Talen: nvt

Literatuurspecialist: Ingeborg van Dusseldorp
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.
Toelichting: Voor deze vraag is gezocht met de volgende concepten: morbus Conn EN adrenal vein sampling Er is gezocht naar systematische reviews en RCTs. Daarnaast is ook gezocht naar observationele studies over diagnostische accuratesse. In de diagnostische set worden 2 van de 5 sleutelartikelen gevonden. (Zhou, Matur) In de SRs en RCTs worden 3 van de 5 sleutelartikelen gevonden. (Yan, Zhou, Dekkers) Het artikel van Zarnegar wordt niet gevonden.
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 17-10-2022 met relevante zoektermen gezocht vanaf 2002, naar systematische reviews, RCTs en diagnostisch observationele studies over adrenal vein sampling. De literatuurzoekactie leverde 364 unieke treffers op.

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	24	14	24
RCTs	22	22	24
Observationele studies, diagnostisch	281	241	316
Overig			
Totaal			364

Zoekstrategie

Embase

No.	Query	Results
#28	#26 OR #27 Diagnostisch, observationeel	281
#27	#18 AND #25	238
#26	#18 AND #24	245
#25	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR	13535553

	observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#24	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#23	#21 OR #22	4
#22	#6 AND #19	3
#21	#6 AND #14	2
#20	#7 AND #19	46
#19	#15 OR #16	46
#18	#14 NOT #16 NOT #15 Diagnostisch	389
#17	#16 NOT #15 RCT	22
#16	#10 AND #13 SR	27
#15	#10 AND #12	24
#14	#10 AND #11	414
#13	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1970810
#12	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	867094
#11	'sensitivity and specificity'/de OR sensitiv*:ab,ti OR specific*:ab,ti OR predict*:ab,ti OR 'roc curve':ab,ti OR 'receiver operator':ab,ti OR 'receiver operators':ab,ti OR likelihood:ab,ti OR 'diagnostic error'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'inter observer':ab,ti OR 'intra observer':ab,ti OR interobserver:ab,ti OR intraobserver:ab,ti OR validity:ab,ti OR kappa:ab,ti OR reliability:ab,ti OR reproducibility:ab,ti OR ((test NEAR/2 're-test'):ab,ti) OR ((test NEAR/2 'retest'):ab,ti) OR 'reproducibility'/exp OR accuracy:ab,ti OR 'differential diagnosis'/exp OR 'validation study'/de OR 'measurement precision'/exp OR 'diagnostic value'/exp OR 'reliability'/exp OR 'predictive value'/exp OR ppv:ti,ab,kw OR npv:ti,ab,kw	9431442
#10	#9 AND [1-1-2002]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	812
#9	#7 AND #8	1451
#8	'adrenal vein sampling'/exp OR 'adrenal vein sampl*':ti,ab,kw OR (('adrenal ven*' NEAR/3 sampl*):ti,ab,kw)	1653
#7	'hyperaldosteronism'/exp OR 'aldosteronism':ti,ab,kw OR 'hyperaldosteron*':ti,ab,kw OR 'hypermineralocorticidism':ti,ab,kw OR 'hypermineralocorticism':ti,ab,kw OR 'mineralcorticoid excess syndrome':ti,ab,kw OR (((morbus OR syndrome OR disease) NEAR/3 conn*):ti,ab,kw)	36488
#6	#1 OR #2 OR #3 OR #4 OR #5 sleutelartikelen	5
#5	is AND adrenal AND venous AND sampling AND necessary AND in AND all AND patients AND with AND hyperaldosteronism AND before AND adrenalectomy AND zarnegar	1
#4	prognosis AND of AND adrenalectomy AND guided AND by AND computed AND tomography AND versus AND adrenal AND vein AND sampling AND in AND patients AND with AND primary AND aldosteronism	1
#3	diagnostic AND accuracy AND of AND adrenal AND imaging AND for AND subtype AND diagnosis AND in AND primary AND aldosteronism AND systematic AND review AND 'meta analysis'	1
#2	consequences AND venous AND sampling AND in AND primary AND hyperaldosteronism AND predictors AND of AND unilateral AND adrenal AND disease	1
#1	adrenal AND vein AND sampling AND versus AND ct AND scan AND to AND determine AND treatment AND in AND primary AND aldosteronism AND dekkers	1

Ovid/Medline

#	Searches	Results
16	13 and (14 or 15) Diagnostisch, observationeel	241
15	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5267013
14	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4268403
13	9 not 11 not 10 Diagnostisch	351
12	11 not 10 RCT	22
11	5 and 8	26
10	5 and 7	14
9	5 and 6 SR	370
8	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1553383
7	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	623514
6	exp "Sensitivity and Specificity"/ or (Sensitiv* or Specific*).ti,ab. or (predict* or ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab. or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or Diagnosis, Differential/ or Validation Study/	7561508
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	731
4	limit 3 to yr="2002 -Current"	774
3	1 and 2	849
2	(adrenal vein sampl* or (adrenal ven* adj3 sampl*)).ti,ab,kf.	965
1	exp Hyperaldosteronism/ or aldosteronism.ti,ab,kf. or hyperaldosteron*.ti,ab,kf. or hypermineralocorticidism.ti,ab,kf. or hypermineralocorticism.ti,ab,kf. or mineralcorticoid excess syndrome.ti,ab,kf. or ((morbus or syndrome) adj3 conn).ti,ab,kf.	11836

Module 3 – Behandeling morbus Conn

Uitgangsvraag
Wat is de plaats van chirurgische behandeling versus medicamenteuze behandeling bij morbus Conn (primair hyperaldosteronisme)?

Inleiding
In de huidige situatie wordt een patiënt met M. Conn (primair hyperaldosteronisme) geopereerd als er een unilaterale aldosteron-overproductie is aangetoond met veneuze bijniervene sampling (AVS). Alle andere patiënten (met bilaterale afwijkingen of normale bijnieren op CT en/of AVS zonder lateralisatie of ongeschikte patiënten voor chirurgie) worden medicamenteus behandeld met een mineralocorticoïd receptor antagonist, eventueel aangevuld met andere antihypertensiva.
Met betrekking tot de behandeling van primair hyperaldosteronisme zijn er verschillende uitkomstmaten van belang: bloeddrukregulatie, kaliumbalans, lange termijn (cardiovasculaire) morbiditeit en mortaliteit en kwaliteit van leven. De vraag is of er verschillen zijn in deze uitkomstmaten tussen geopereerde patiënten en medicamenteus behandelde patiënten.

Search and select
A systematic review of the literature was performed to answer the following question: What are the advantages and disadvantages of surgery versus medication for the treatment of patients with M. Conn (primary aldosteronism) on blood pressure control, number of antihypertensive drugs, normokalemia, (long-term) cardiovascular morbidity and mortality and quality of life.

P (Patients)	Patients with primary aldosteronism (M. Conn)
I (Intervention)	Adrenal surgery
C (Control)	Medication
O (Outcomes)	Blood pressure control, number of antihypertensive drugs, normokalemia, (long-term) cardiovascular morbidity and mortality, cardiovascular events and quality of life

<u>Relevant outcome measures</u>
The guideline development group considered *blood pressure control, cardiovascular morbidity and mortality, cardiovascular events and quality of life as a* critical outcome measure for decision making and *number of anti-hypertensive drugs and normokalemia* as an important outcome measure for decision making.

The guideline development group defined the outcome measures as follows:
- Blood pressure control: Systolic and diastolic blood pressure.
- Number of antihypertensive drugs: daily defined dose of drugs to control hypertension.
- Normokalemia: Normalization of potassium levels in the blood.

A priori, the working group did not define the outcome measures cardiovascular morbidity and mortality, cardiovascular events and quality of life, but used the definitions used in the studies.

The working group defined the following differences as a minimal clinically (patient) important difference:

Dichotomous outcomes (absolute difference)

- Normokalemia: ≥5%
- Cardiovascular morbidity ≥1%
- Cardiovascular mortality: ≥1%
- Cardiovascular events: ≥5%

Continuous outcomes (mean difference):

- Blood pressure control: 10mmHg
- Number of antihypertensive drugs: daily defined dose of >1
- Quality of life: EQ5D MCID: 0.18 and SF-36: 5.00 (Coretti, 2014; Ogura, 2020)

Search and select (Methods)

Initially the databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 15 February 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 114 hits. Studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICO;
- The intervention and comparison had to be as defined in the PICO;
- One or more reported outcomes had to be as defined in the PICO;
- Research type: Systematic review, randomized-controlled trial, prospective or retrospective observational cohort studies;
- Articles written in English or Dutch

Seven studies were initially selected based on title and abstract screening. After reading the full text, five studies were excluded (see the table with reasons for exclusion under the tab Methods). The review of Satoh (2019) and an RCT (Velema, 2018) were included. An update of the search was performed to search for observational studies after the search date of Satoh (2019) (24 August 2017). The updated systematic literature search resulted in another 542 hits. Twenty-seven studies were selected based on title and abstract screening and fifteen studies were excluded (see the table with reasons for exclusion under the tab Methods), twelve additional studies were included.

Results

One systematic review, one RCT and twelve additional cohort 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

Satoh (2019) performed a systematic review of the literature. Randomized Controlled Trials (RCT), prospective cohort studies and retrospective cohort studies which compared the operative treatment with the medical treatment in patients with primary aldosteronism, were included in this review. Other inclusion criteria were that a study had to provide values (means with standard deviation) of at least one of the following variables: Left ventricular mass (LVM), serum potassium, systolic blood pressure (SBP), glomerular filtration ratio (GFR), the number of oral antihypertensive agents or incidence of cardiovascular events. No exclusion criteria were reported. The search was performed to articles published between 1985 and 2017. Satoh (2019) included sixteen studies in the review. All studies were cohort studies. Four studies with 2073 patients were included in the meta-analysis of cardiovascular events. Eight studies with 903 patients were included in the systolic blood pressure meta-analysis. Five studies with a total of 499 patients were included in the hypokalemia analysis

and three studies with 265 patients were included in the meta-analysis of the number of antihypertensive agents.

Velema (2018) performed a post hoc comparative effectiveness study within the Subtyping Primary Aldosteronism: A Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography Scan (SPARTACUS) trial. Inclusion data were reported in the SPARTACUS trial (Dekkers, 2016). Regarding this post hoc study patients who underwent adrenalectomy were compared with patients who underwent mineralocortoid receptor antagonist (MRA) treatment. Both the adrenalectomy group and the MRA treatment group, consisted of 92 patients. Mean age in the adrenalectomy group was 51.8 years and 71.7% was male. Mean age in the MRA treatment group was 54.4 years and 84.8% was male. Median Body Mass Index (BMI) was 27.5 kilogram per square meter in the adrenalectomy group and 29.4 kilogram per square meter in the MRA treatment group. Mean serum potassium level in the adrenalectomy group was 3.5 mEq per liter and in the MRA treatment group 3.6 mEq per liter. Velema (2018) reported quality of life using the EQ-5D, which comprises five questions, and the 36-item Short Form Health Survey (SF-36) which consisted of eight subscales which are reported separately. Also, the physical component summary (PCS) and mental component summary (MCS) of the SF-36 are reported. A higher score indicates a better health condition.

Araujo Castro (2022) performed a retrospective cohort study using patient reports from the Spanish Primary Aldosteronism Registry of the Spanish Endocrinology and Nutrition Society (SPAIN-ALDO) with a follow-up between 2018 and 2020. Patients who underwent adrenalectomy or were under medical treatment with Mineralocorticoid Receptor Antagonist (MRA) and who had clinical, hormonal, and biochemical information during follow-up, were included. Patients with confirmed co-secretion of cortisol were excluded. The adrenal surgery group consisted of 100 patients with unilateral PA, a mean age of 52.7 years and a mean Body Mass Index (BMI) of 29.1 kilogram per square meter. The medication group consisted of 168 patients with bilateral PA, a mean age of 54.7 years and mean BMI of 30.0 kilogram per square meter. The adrenal surgery group consisted of 54 women (54.6%) and 63 patients (76.8%) experienced grade two or higher hypertension. The medication group consisted of 70 women (41.7%) and 108 patients (70.6%) experienced grade two or higher hypertension. Araujo Castro (2022) reported systolic blood pressure, diastolic blood pressure, cardiovascular events and number of antihypertensive drugs.

Buffolo (2020) performed a prospective cohort study including patients from the QUALITO study in Italy. The total cohort consisted of 70 patients with primary aldosteronism and 70 matched patients with essential hypertension, only data regarding patients with primary aldosteronism (PA), are taken into account. Mean age of the PA patients was 52 years and 35.7% was female. Mean BMI was 25.9 and 67 patients (95.7%) had type 2 diabetes. There were 37 patients included with unilateral PA who underwent laparoscopic adrenalectomy and 30 patients with unilateral or bilateral PA who received mineralocorticoid receptor antagonist (MRA) treatment. The MRA treatment consisted of spironolactone (n=14) or potassium canrenoate (n=16).
Buffolo (2020) reported systolic blood pressure, diastolic blood pressure, number of antihypertensive drugs and quality of life. Quality of life was measured using the 36-item Short Form Health Survey (SF-36) which consisted of eight subscales which are reported separately. A higher score indicates a better health condition.

Chen (2021) performed a prospective cohort study including patients with hypertension and primary aldosteronism in the inpatient ward from November 2018 to July 2020. Patients

with other forms of secondary hypertension, ischemic heart disease, valvular heart disease, cardiomyopathy, pacemaker implantation, atrial fibrillation, or suboptimal echocardiographic windows, were excluded. They included 39 patients who underwent unilateral adrenalectomy. The mean age was 49.4 years and mean BMI was 25.7 kilogram per square meter. There were 28 patients with bilateral PA who underwent treatment with mineralocorticoid receptor antagonist (MRA) with a mean age of 48.8 years and mean BMI of 26.8 kilogram per square meter. Median plasma renin activity in the surgery group was 0.27 nanogram per millilitre per hour and 0.84 nanogram per millilitre per hour in the MRA treatment group. Chen (2021) reported systolic blood pressure and diastolic blood pressure.

Haze (2021) performed a retrospective cohort study using data from the Japan Rare/Interactable Adrenal Disease Study (JRAS). Patients aged between 20 and 90 years, enrolled in JRAS between 2006 and 2019, diagnosed with PA based on guidelines of the Japan Endocrine Society and Japanese Society of Hypertension, records with assessment of of plasma aldosterone concentration, plasma renin activity and blood pressure before treatment, treatment with unilateral adrenalectomy or MRA for unilateral or bilateral PA between month zero and six and observation data for more than six months from baseline, were included. The adrenalectomy group consisted of 740 patients with a mean age of 51.5 years, 49.7 percent was female and mean BMI was 24.2 kilograms per square meter. The MRA treatment group consisted of 1247 patients with a mean age of 54.2 years, 53.4 percent was female and mean BMI was 25.1 kilograms per square meter. Mean duration of hypertension in the adrenalectomy group was 10.1 years and in the MRA treatment group 8.0 years. Haze (2021) reported on systolic blood pressure and diastolic blood pressure.

Katabami (2019) performed a retrospective cohort study using data from the Japan Primary Aldosteronism Study (JPAS). Patients enrolled in the JPAS between January 2006 and October 2016 with primary aldosteronism with confirmed unilateral subtype. Patients were excluded in case of a bilateral subtype, unsuccessful adrenal vein sampling (AVS), AVS without adrenocorticotropic hormone stimulation, missing follow-up data, incomplete data on blood pressure and/or antihypertensive drugs or if patients in the medically treated group missed out on receiving MRAs. The unilateral adrenalectomy group consisted of 63 patients with median age of 54.0 years, 46% female, median duration of hypertension of 9.0 years and 17.3% diabetic. The mineralocortoid receptor antagonist (MRA) treatment group consisted of 276 patients with median age of 60.0 years, 32% female, median duration of hypertension of 12.5 years and 20.6% diabetic. Because groups were not comparable at baseline, propensity score matching was used to reduce bias associated with different prevalence of some baseline characteristics within the treatment groups. Therefore, in the analysis 55 patients in the adrenalectomy group and 55 patients in the MRA treatment group were included. Katabami (2019) reported systolic blood pressure, diastolic blood pressure, serum potassium normalization rate and daily defined dose of antihypertensive drugs. There was no clear definition of normalization of serum potassium rate.

Meng (2019) performed a retrospective cohort study, with data from the Fuwai Hospital in China. Patients who were hospitalized between January 2016 and December 2017, who had successful AVS proven unilateral PA, were included in this study. Surgical treatment consisted of total or partial laparoscopic adrenalectomy and medical treatment consisted of mineralocortoid receptor antagonist (MRA) treatment by spironolactone. Mean age in the adrenalectomy group was 44.6 years, 57.1% was female and mean body mass index (BMI) was 24.2 kilogram per square meter. Mean age in the MRA treatment group was 50.5 years, 33.3% was female and mean BMI was 27.0 kilogram per square meter. Mean duration of hypertension in the adrenalectomy group was 8.3 years and in the MRA treatment group

13.6 years. In the adrenalectomy group no patients had diabetes mellitus, in the MRA treatment group five patients (16.7%) had diabetes mellitus. Meng (2019) reported systolic blood pressure, diastolic blood pressure, number of antihypertensive drugs and number of patients with hypokalemia. There was no clear definition of hypokalemia.

Murck (2021) performed a retrospective cohort study using data from the German Conn registry. Patients with newly diagnosed primary aldosteronism were included. Unilateral adrenalectomy was performed in case of a unilateral tumor in 75 patients. Mineralocorticoid receptor antagonist (MRA) treatment, mainly with spironolactone was used for bilateral hyperplasia of the adrenal gland in 90 patients. The study stratified data according to gender. Therefore, baseline characteristics were not reported for patients in the adrenalectomy and the MRA treatment group. Regarding the scope of this summary, only systolic blood pressure and diastolic blood pressure were reported.

Nakamaru (2021) performed a retrospective cohort study using data from the Japan Primary Aldosteronism Study (JPAS). Patients aged between 20 and 90 years with PA who underwent adrenal vein sampling (AVS) were included. Patients with no follow-up data regarding blood pressure or estimated glomerular filtration rate, were excluded. The adrenalectomy treatment group consisted of 622 patients and the mineralocorticoid receptor antagonist (MRA) treatment group consisted of 233 patients. Nakamaru (2021) stratified data according to age (< 65 years versus ≥ 65 years) therefore not all baseline and outcome data were available regarding the scope of this summary. Nakamaru (2021) reported number of cardiovascular events.

Puar (2020) performed a retrospective cohort study using data from two referral centers in Singapore between 2000 and 2019. Patients with confirmed unilateral PA by AVS and patients with likely unilateral PA by clinical prediction score, were included. Patients without adequate follow-up for at least six months post-treatment and patients with baseline estimated glomerular filtration rate (eGFR) under 45 milliliter per minute per 1.73 square meter, were excluded. The unilateral adrenalectomy group consisted of 86 patients with mean age of 51.0 years and mean eGFR of 90.7 ml/min/1.73 m^2. The mineralocorticoid receptor antagonist (MRA) treatment group consisted of 68 patients with a mean age of 55.0 years and mean eGFR of 83.8 ml/min/1.73 m^2. Puar (2020) reported systolic blood pressure, diastolic blood pressure, number of antihypertensive drugs and a composite outcome for cardiovascular events, consisting of acute myocardial infarction, coronary revascularization or coronary artery bypass graft, admission for congestive cardiac failure, incidence of atrial fibrillation or stroke.

Tan (2021) performed a prospective cohort study using data from the Changi General Hospital. Patients of age eighteen years or older, with confirmed diagnosis of PA and completion of baseline questionnaires, were included. Patients with adrenal carcinoma, severe or terminal co-morbidity that interfered with possible treatment or Health-Related Quality of Life (HRQoL) or glucocorticoid-remediable aldosteronism, were excluded. The unilateral adrenalectomy group consisted of 21 patients with a mean age of 48.1 years, mean body mass index of 26.9 kilogram per square meter and 38.1 percent was female. The medical treatment group consisted of 13 patients with a mean age of 56.4 years, mean body mass index of 28.6 kilogram per square meter and 15.4 percent was female.
Tan (2021) reported quality of life using the EQ-5D and the SF-36. The 36-item Short Form Health Survey (SF-36) consists of eight subscales, which were reported separately. A higher score indicates a better health condition.

Wada (2017) performed a retrospective cohort study using data from the West Japan Adrenal Vein Sampling study (WAVES-J). Patients with PA who underwent AVS from January 2006 to December 2013 and who had at least one of the recordings of data after treatment, were included. Patients who did not take Mineralocorticoid Receptor Antagonist after diagnosis of PA, were excluded. The surgery comprised unilateral adrenalectomy. The medical treatment comprised Mineralocorticoid Receptor Antagonist (MRA) treatment. The adrenalectomy group consisted of 142 patients with a mean age of 53 years. Of these patients 50% was female, median aldosterone renin ratio was 1085 and mean serum potassium level was 3.3 m Eg l^{-1} .
Wada (2017) reported systolic blood pressure, diastolic blood pressure, number of antihypertensive drugs and hyperkalemia.

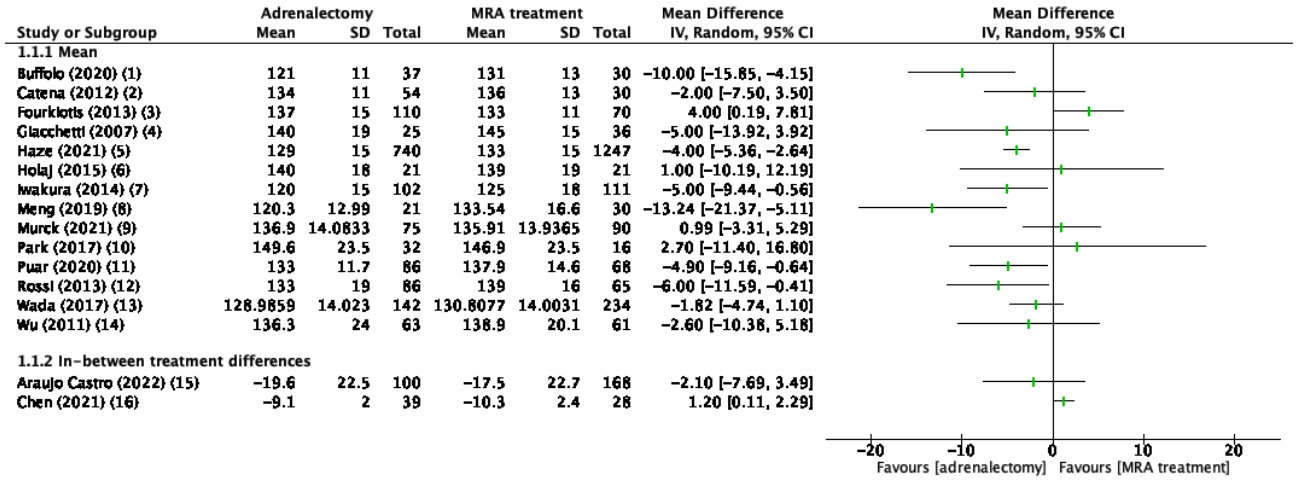
Zavatta (2019) performed a prospective cohort study with patients from the Endocrinology unit of the S. Orsola-Malpighi University Hospital of Bologna, Italy. Patients diagnosed with PA according to current guidelines were included in the study undergoing a unilateral adrenalectomy or treatment with aldosterone antagonist (canrenone). The control group in this study consisted of consecutive hypertensive patients. Regarding the scope of this summary, only data and outcomes regarding patients with PA, were reported. The adrenalectomy group consisted of 12 patients, the aldosterone antagonist treatment group consisted of 33 patients. Because in this study patients with PA were compared to patients with hypertension, no baseline data of the adrenalectomy versus medication group, were available. Zavatta (2019) reported the number of anti-hypertensive drugs.

Results

Blood pressure control

Systolic blood pressure

Systolic blood pressure was reported in eight studies in the review of Satoh (2019) and nine additional studies (**Araujo Castro, 2022; Buffolo, 2020; Chen, 2021; Haze, 2021; Katabami, 2019; Meng, 2019; Murck, 2021; Puar, 2020; Wada, 2017**). Two studies reported in-between treatment differences in systolic blood pressure (**Araujo Castro, 2022; Chen, 2021**). The results of the studies that presented the mean systolic blood pressure, are presented in **Figure 1**. Because of the heterogeneity of the studies due to difference in study population, intervention and duration of follow-up, the pooled results are not displayed.
Katabami (2019) reported median between treatment difference in the adrenalectomy group of -9.0 mmHg (95%CI -22.0 – -3.0) and in the MRA treatment group -5.0 mmHg (95%CI -25.0 – 6.0).



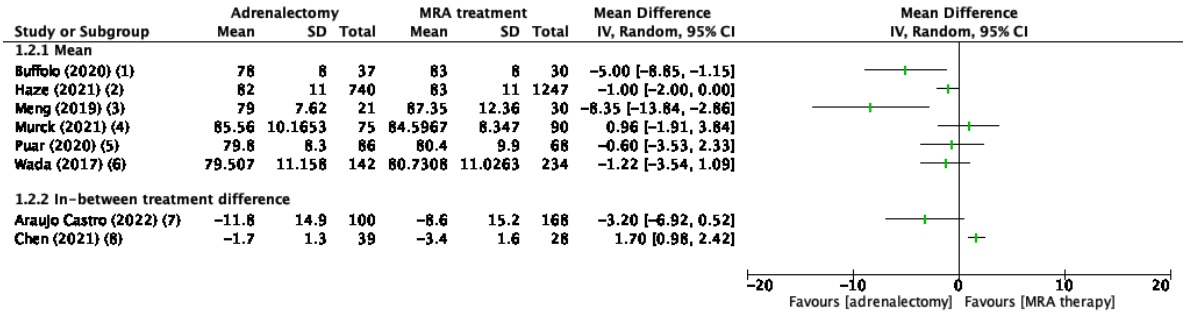
Footnotes
(1) FU 6 months
(2) Data extracted from Satoh (2019)
(3) Data extracted from Satoh (2019)
(4) Data was extrated from Satoh (2019)
(5) Median FU 1048 days for intervention group
(6) Data extracted from Satoh (2019)
(7) Data extracted from Satoh (2019)
(8) FU 22.05 months for adrenalectomy group
(9) FU 1 year
(10) Data extracted from Satoh (2019)
(11) FU 5.7 years
(12) Data extracted from Satoh (2019)
(13) FU 6 months
(14) Data extracted from Satoh (2019)
(15) FU 2 years
(16) FU 6 months

Figure 1. Outcome systolic blood pressure with adrenalectomy versus MRA
Z: p-value of pooled effect; df: degrees of freedom, I^2: statistical heterogeneity, CI: confidence interval

Diastolic blood pressure

Diastolic blood pressure was reported in nine studies (**Araujo Castro, 2022; Buffolo, 2020; Chen, 2021; Haze, 2021; Katabami, 2019; Meng, 2019; Murck, 2021; Puar, 2020; Wada, 2017**). Two studies reported in-between treatment differences in diastolic blood pressure (**Araujo Castro, 2022; Chen, 2021**). The results of the studies that presented the mean systolic blood pressure, are presented in **Figure** 2. Because of the heterogeneity of the studies due to difference in study population, intervention and duration of follow-up, the pooled results are not displayed.

Katabami (2019) reported median between treatment difference in the adrenalectomy group of -4.5 mmHg (95%CI -12.0 – 7.0) in the adrenalectomy group and -7.0 mmHg (95%CI -13.0 – 4.0) in the MRA treatment group.

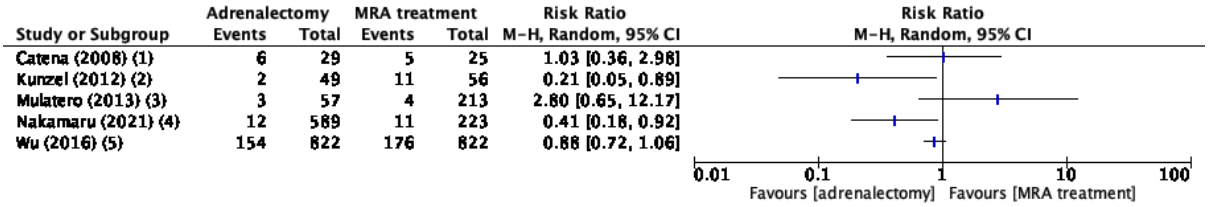


Footnotes
(1) FU 6 months
(2) Median FU 1048 days in intervention group
(3) FU 22.05 months in intervention group
(4) FU 1 year
(5) FU 5.7 years
(6) FU 6 months
(7) FU 2 years
(8) FU 6 months

Figure 2. Outcome diastolic blood pressure with adrenalectomy versus MRA
Z: p-value of pooled effect; df: degrees of freedom, I^2: statistical heterogeneity, CI: confidence interval

Cardiovascular morbidity and mortality
None of the included studies reported cardiovascular morbidity and mortality.

Cardiovascular events
Four studies in the review of Satoh (2019) and three additional studies reported cardiovascular events (Aruajo Castro, 2022; Nakamaru, 2021; Puar, 2020). The review of **Satoh (2019)** and **Nakamaru (2021)** reported number of cardiovascular events with a relative risk. Because of the heterogeneity of the studies due to difference in study population, intervention and duration of follow-up, the pooled results are not displayed (figure 3).
Araujo Castro (2022) reported new cardiovascular events using a hazard ratio. In the adrenalectomy group two events (3.9%) were reported and in the MRA treatment group seven events (6.4%) were reported (HR 0.5 [95%CI 0.1-2.2]).
Puar (2020) reported composite cardiovascular events using a hazard ratio (HR 0.93 [95%CI 0.32-2.67]).



Footnotes
(1) Data extracted from Satoh (2019)
(2) Data extracted from Satoh (2019)
(3) Data extracted from Satoh (2019)
(4) FU 36 months
(5) Data extracted from Satoh (2019)

Figure 3. Outcome cardiovascular events with adrenalectomy versus MRA
Z: p-value of pooled effect; df: degrees of freedom, I^2: statistical heterogeneity, CI: confidence interval

Quality of life
Three studies reported quality of life (Buffolo, 2020; Velema, 2018; Tan, 2021).
Velema (2018) reported SF-36 subscale scores as mean difference with a Dutch reference population for the adrenalectomy and the MRA treatment group. The physical component summary (PCS) of the SF-36 in the adrenalectomy was 2.4 (95%CI 0.3-4.5) and in the MRA treatment group -1.5 (95%CI -4.0-0.9). The mental component summary (MCS) in the

adrenalectomy group was -0.2 (95%CI -2.4-2.1) and in the MRA treatment group -4.0 (95%CI -6.3 – -1.8).
The studies of **Buffolo (2020)** and **Tan (2021)** reported mean scores in the treatment groups for the different subscales (**Figure 4**). Because of the heterogeneity of the studies due to difference in study population, intervention and duration of follow-up, the pooled results are not displayed, and the results of Velema (2018) were not added to this figure.

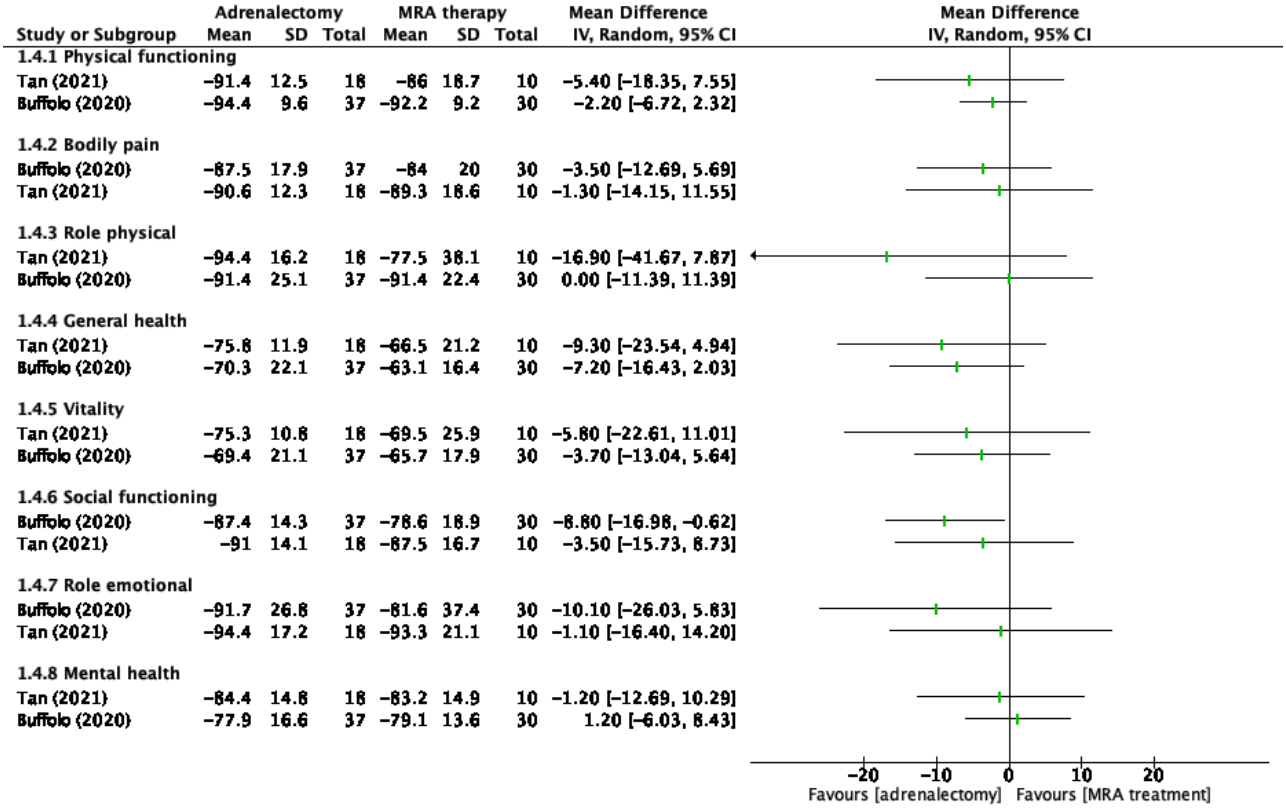


Figure 4. Outcome quality of life (SF-36 subscales) with adrenalectomy versus MRA
Z: p-value of pooled effect; df: degrees of freedom, I^2: statistical heterogeneity, CI: confidence interval

Two studies also reported the EQ-5D scores (Velema, 2018; Tan, 2021). **Velema (2018)** reported adjusted odds ratios for reporting problems on the EQ-5D during follow-up for adrenalectomy treatment versus MRA treatment.

Table 3. Odds Ratios EQ-5D, Velema (2018)

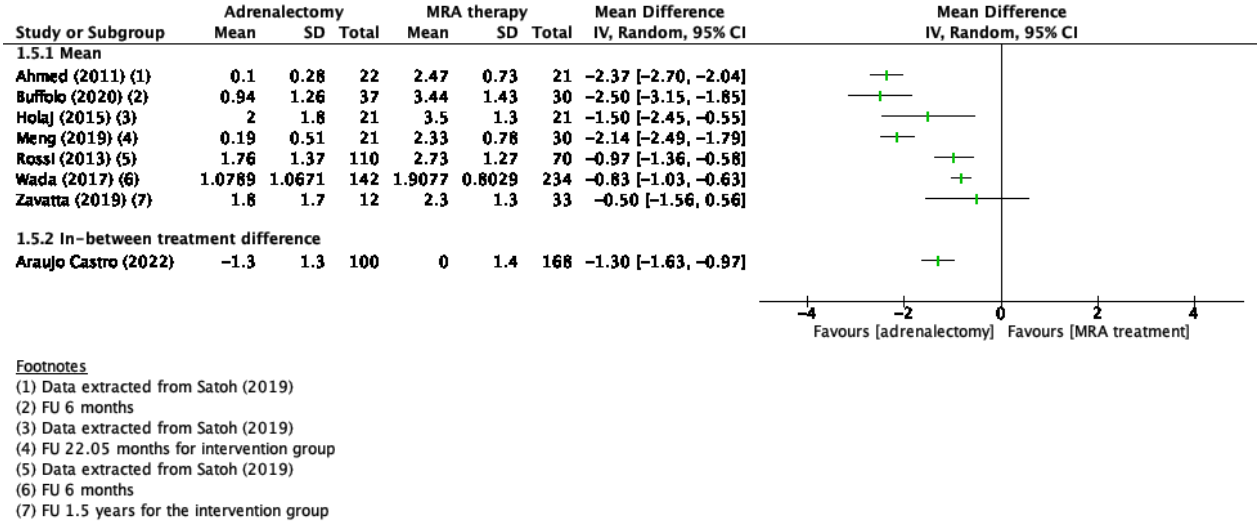
Dimension of EQ-5D	Adrenalectomy/MRA, Adjusted Odds Ratio (95%CI)
Mobility	0.52 (0.23-1.20)
Self-care	0.14 (0.01-2.50)
Usual activities	0.35 (0.17-0.75)
Pain/discomfort	0.52 (0.30-0.91)
Anxiety/depression	0.79 (0.39-1.60)

Tan (2021) reported that the median EQ-5D index score in the adrenalectomy group was 1.00 (IQR 1.00-1.00) and in the MRA treatment group 1.00 (IQR 0.838-1.00).

Number of antihypertensive drugs

Number of antihypertensive drugs was reported in three studies in the review of Satoh (2019) and seven additional studies (Araujo Castro, 2022; Buffolo, 2020; Katabami, 2019; Meng, 2019; Puar, 2020; Wada, 2017; Zavatta, 2019).

The review of **Satoh (2019)**, **Buffolo (2020)**, **Meng (2019)** and **Wada (2017)** reported mean number of antihypertensive drugs. **Araujo Castro (2022)** reported in-between treatment difference in number of antihypertensive drugs. Because of the heterogeneity of the studies due to difference in study population, intervention, reporting of the outcome and duration of follow-up, the pooled results are not displayed (**Figure 5**).



Footnotes
(1) Data extracted from Satoh (2019)
(2) FU 6 months
(3) Data extracted from Satoh (2019)
(4) FU 22.05 months for intervention group
(5) Data extracted from Satoh (2019)
(6) FU 6 months
(7) FU 1.5 years for the intervention group

Figure 5. Outcome number of hypertensive drugs with adrenalectomy versus MRA
Z: p-value of pooled effect; df: degrees of freedom, I^2: statistical heterogeneity, CI: confidence interval

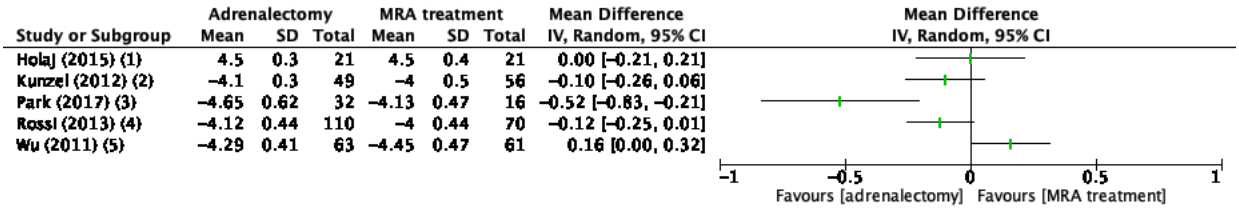
Katabami (2019) reported median daily defined dose of antihypertensive drugs of -1.0 (IQR -1.9-0.0) in the adrenalectomy group and 0.5 (IQR -0.1-2.0) in the MRA treatment group.
Puar (2020) reported median change in number of antihypertensive drugs of -1.0 (IQR -2.0-0.0) in the adrenalectomy group and 0.0 (IQR -1.0-1.0) in the MRA treatment group.

Normokalemia

One study reported normalization of serum potassium levels (Katabami, 2019). One study described average serum potassium levels at follow-up in the different treatment groups (Satoh, 2019) and one study reported percentage of patients with hypokalemia at follow-up in both groups (Meng, 2019).

Katabami (2019) reported normalization of serum potassium levels in 55 patients (100%) in the adrenalectomy group and in 50 patients (90.9%) in the MRA treatment group.

The review of **Satoh (2019)** reported mean end-of-study serum potassium levels in the adrenalectomy group and MRA treatment group. Because of the heterogeneity of the studies due to difference in study population, intervention, reporting of the outcome and duration of follow-up, the pooled results are not displayed.



Footnotes
(1) Data extracted from Satoh (2019)
(2) Data extracted from Satoh (2019)
(3) Data extracted from Satoh (2019)
(4) Data extracted from Satoh (2019)
(5) Data extracted from Satoh (2019)

Figure 6. Outcome normokalemia with adrenalectomy versus MRA
Z: p-value of pooled effect; df: degrees of freedom, I^2: statistical heterogeneity, CI: confidence interval

Meng (2019) reported the percentage of patients with hypokalemia at follow-up. In the adrenalectomy group no patients (0%) experience hypokalemia, in the MRA treatment group 4 patients (13.3%) experienced hypokalemia.

Level of evidence of the literature
The level of evidence of observational cohort studies is considered low according to the GRADE methodology. Therefore, the level of evidence of these cohort studies starts at low GRADE.

Blood pressure control
The level of evidence regarding the outcome measure **blood pressure control** was downgraded by three levels because of study limitations (-1; risk of bias regarding confounding reporting, confounding analysis and selection bias), conflicting results (-1; inconsistency because of clinical and methodological heterogeneity) and number of included patients (-1; imprecision because of low sample size). The level of evidence was therefore graded as very low.

Cardiovascular morbidity and mortality
None of the included studies reported cardiovascular morbidity and mortality.

Cardiovascular events
The level of evidence regarding the outcome measure **cardiovascular events** was downgraded by three levels because of study limitations (-1; risk of bias regarding confounding report, confounding analysis and adequate follow-up); conflicting results (-1; inconsistency because of clinical and methodological heterogeneity) and number of included patients (-1; imprecision because of low sample size and small number of events per arm). The level of evidence was therefore graded as very low.

Quality of life
The level of evidence regarding the outcome measure **quality of life** was downgraded by two levels because of study limitations (-1; risk of bias regarding selection bias, assessment of exposure, confounding assessment and analysis) and number of included patients (-1; imprecision because of low sample size and the confidence interval are including the possibility of a positive effect or no effect).
The level of evidence was therefore graded as very low.

Number of anti-hypertensive drugs
The level of evidence regarding the outcome measure **number of antihypertensive drugs** was downgraded by two levels because of study limitations (-1; risk of bias regarding

selection bias, confounding assessment, confounding analysis and difference in follow-up) and number of included patients (-1; imprecision because of low sample size).
The level of evidence was therefore graded as very low.

Normokalemia
The level of evidence regarding the outcome measure **normokalemia** was downgraded by three levels because of study limitations (-1; risk of bias regarding confounding assessment and analysis), conflicting results (-1; inconsistency because of clinical and methodological heterogeneity) and number of included patients (-1; imprecision because of low sample size). The level of evidence was therefore graded as very low.

Conclusions
Blood pressure control

Very low GRADE	The evidence is very uncertain about the effect of adrenalectomy on blood pressure control compared with MRA treatment in patients with primary aldosteronism. *Sources: Satoh, 2019; Araujo Castro, 2022; Buffolo, 2020; Chen, 2021; Haze, 2021; Katabami, 2019; Meng, 2019; Murck, 2021; Puar, 2020; Wada, 2017*

Cardiovascular morbidity and mortality

No GRADE	No evidence was found regarding the effect of adrenalectomy on cardiovascular morbidity and mortality compared with MRA treatment in patients with primary aldosteronism. *Source: -*

Cardiovascular events

Very low GRADE	The evidence is very uncertain about the effect of adrenalectomy on cardiovascular events compared with MRA treatment in patients with primary aldosteronism. *Sources: Satoh, 2019; Aruajo Castro, 2022; Nakamaru, 2021; Puar, 2020*

Quality of life

Very low GRADE	The evidence is very uncertain about the effect of adrenalectomy on quality of life compared with MRA treatment in patients with primary aldosteronism. *Sources:* Buffolo, 2020; Velema, 2018; Tan, 2021

Number of antihypertensive drugs

Very low GRADE	The evidence is very uncertain about the effect of adrenalectomy on number of antihypertensive drugs compared with MRA treatment in patients with primary aldosteronism. *Sources:* Satoh, 2019; Araujo Castro, 2022; Buffolo, 2020; Katabami, 2019; Meng, 2019; Puar, 2020; Wada, 2017; Zavatta, 2019

Normokalemia

Very low GRADE	The evidence is very uncertain about the effect of adrenalectomy on normokalemia compared with MRA treatment in patients with primary aldosteronism. *Sources:* Satoh, 2019; Katabami, 2019; Meng, 2019

Overwegingen – van bewijs naar aanbeveling

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

Voor drie van de vier cruciale uitkomstmaten (bloeddrukcontrole, cardiovasculaire events en kwaliteit van leven) werden resultaten gerapporteerd in de geïncludeerde studies. Voor de uitkomst cardiovasculaire morbiditeit en mortaliteit, zijn geen resultaten gerapporteerd. Zeventien studies rapporteerden systolische bloeddruk en negen studies rapporteerden diastolische bloeddruk welke verschillende effecten lieten zien. De meeste studies lieten een effect zien in het voordeel van de chirurgische behandeling lieten zien. Slechts twee studies toonden lieten een klinisch relevant effect zien van 10mmHg of meer in het voordeel van de chirurgische behandeling.
Zeven studies rapporteerde cardiovasculaire events en lieten verschillende effecten zien. Vier studies vier studies rapporteerden een positief effect in het voordeel van de chirurgische behandeling. Daarnaast rapporteerden twee studies geen effect en één studie rapporteerde een negatief effect.
Drie studies rapporteerden kwaliteit van leven met behulp van de SF-36 (Buffolo, 2020; Velema, 2018; Tan, 2021). Voor de subschalen fysiek functioneren, pijn, algemene gezondheid, vitaliteit en sociaal en emotioneel functioneren was er een voordeel te zien voor de chirurgische behandeling. Voor de subschaal mentale gezondheid was er geen verschil te zien tussen beide behandelingen. Twee studies (Velema, 2018; Tan, 2021) hebben daarnaast ook EQ-5D gebruikt om kwaliteit van leven te meten waarbij er één studie wel een verschil vond en één studie geen verschil vond tussen de chirurgische behandeling en medicamenteuze behandeling. Dit kan verklaard worden tussen het verschil in studie populaties en de manier van rapporteren van de uitkomsten.

De overall bewijskracht voor alle uitkomstmaten was zeer laag omdat er in sommige gevallen mogelijk sprake was van selectie bias. Daarnaast zijn er enkele studies die de medicamenteuze behandeling niet goed beschreven hebben waardoor het niet duidelijk is wat patiënten precies voor medicatie ontvangen hebben. In veel studies zijn mogelijke covariabelen niet beschreven en/of is er niet gecorrigeerd voor mogelijke confounding. Daarnaast was er sprake van inconsistente resultaten tussen de studies vanwege verschillende studiepopulaties. Sommige studies hebben alleen patiënten met unilateraal primair hyperaldosteronisme geïncludeerd, terwijl de meeste studies zowel patiënten met unilateraal als bilateraal primair hyperaldosteronisme hebben geïncludeerd. Daarnaast verschilde de interventie ook per studie. In sommige studies werd de chirurgische behandeling alleen toegepast bij patiënten met unilateraal primair hyperaldosteronisme en de medicamenteuze behandeling bij bilateraal of unilateraal primair hyperaldosteronisme.

De hoofdvraag in deze module is of adrenalectomie te verkiezen is boven medicamenteuze therapie bij de behandeling van unilateraal primair hyperaldosteronisme (PHA) met betrekking tot effecten op (a) bloeddruk, (b) kaliumconcentratie, (c) cardiovasculaire morbiditeit en mortaliteit, (d) aantal antihypertensiva en (d) kwaliteit van leven.
Bij analyse van de beschikbare literatuur lijkt adrenalectomie een betere uitkomst te hebben op deze vier eindpunten dan medicamenteuze therapie. Dit wordt ook zo beschreven in een

recente meta-analyse (Chen, 2022). Er zijn echter diverse factoren die de bewijskracht minder overtuigend maken:

- Heterogeniteit in de verschillende studies met betrekking tot patiënten selectie, uitvoering van de medicamenteuze therapie, follow-up duur etc.
- Verschillen in baseline karakteristieken tussen chirurgische en medicamenteus behandelde patiënten. Bijvoorbeeld in sommige studies zijn patiënten ouder, hebben diabetes en/of een hogere BMI in de medicamenteus behandelde groep
- Het voordeel van adrenalectomie is waarschijnlijk minder bij ouderen (Chen, 2022), mogelijk omdat zij al langer bloot hebben gestaan aan hypertensie en teven ook al cardiovasculaire comorbiditeit hebben. Dat jongere patiënten meer profijt hebben van adrenalectomie wordt ook gesuggereerd in de studie van Williams (2017).
- Veelal retrospectieve studies en het ontbreken van prospectieve, gerandomiseerde trials

Daarnaast zijn er twee conceptuele overwegingen die in ogenschouw genomen moeten worden. Allereerst wordt in alle studies niet de biochemische effectiviteit van mineralocorticoid receptor (MR) blokkade geëvalueerd. Bij effectieve MR blokkade dient de renine concentratie te stijgen tot in het normale gebied. Eén studie laat inderdaad zien dat bij patiënten met PHA die behandeld worden met MR blokkade er een verhoogde cardiovasculaire morbiditeit bij een onderdrukt renine vergeleken met patiënten met een normaal renine (Hundemer, 2018). Het is goed voor te stellen dat in de verrichtte studies bij een deel van de patiënten onvoldoende MR blokkade gegeven is waardoor er voortschrijdende negatieve effecten aanhielden als gevolg van van aldosteron overschot. Toekomstige studies zullen dus renine-geleide MR blokkade moeten evalueren.
De tweede conceptuele overweging sluit hier op aan. Adrenalectomie leidt vrijwel altijd tot volledige normalisatie van aldosteron concentraties. Bij medicamenteuze MR blokkade blijven echter chronisch verhoogde aldosteron concentraties bestaan. Ook al zou de MR blokkade leiden tot normale renine waarden (zie bovenstaande) dan zouden chronisch verhoogde aldosteron waarden theoretisch toch schadelijke effecten kunnen hebben. Zo is bijvoorbeeld niet bekend of MR blokkade even effectief is in ieder weefsel, differentiële effecten lijken meer voor de hand te liggen. En om het nog verder te nuanceren, het is ook niet bekend wat voor een bepaald individu een normaal renine is en zou een patiënt die met MR blokkade een laag-normaal renine bereikt nog steeds onder behandeld kunnen zijn.
Ten opzichte van medicamenteuze therapie geeft adrenalectomie een snelle definitieve remissie en maakt het in feite bovenstaande discussie overbodig.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
Bij de beslissing tot chirurgische of medicamenteuze behandeling van primair hyperaldosteronisme dient de voorkeur van de patiënt in ogenschouw genomen te worden (‘samen beslissen’). Voor- en nadelen van beide behandelmodaliteiten moeten vooraf met de patiënt besproken worden waarbij deze een persoonlijke afweging kan maken. Factoren die aan bod moeten komen zijn o.a. effectiviteit van de behandeling, operatie risico, bijwerkingen van medicatie en follow-up duur.

<u>Kosten (middelenbeslag)</u>
Er zijn geen kosten-baten analyse gegevens voorhanden van een chirurgische versus medicamenteuze behandeling van primair hyperaldosteronisme. Echter wanneer een patiënt langduriger of zelfs levenslang onder controle blijft in tweede of derde lijn ten behoeve van de medicamenteuze behandeling, is de verwachting dat de kosten hoger zullen zijn dan een eenmalige operatie. Dit betreft kosten voor geneesmiddelen, medisch-specialistische controle en laboratoriumonderzoek.

Aanvaardbaarheid, haalbaarheid en implementatie

In centra waar bijnieroperaties uitgevoerd worden conform de geldende afspraken en met de aanwezigheid van een multidisciplinair team met bijnierexpertise, zijn geen beperkingen te verwachten met betrekking tot aanvaardbaarheid, haalbaarheid en implementatie.

Aanbeveling

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

Op grond van de huidige literatuur, ofschoon het bewijs beperkt is, gaat de voorkeur van behandeling van unilateraal PHA uit naar een adrenalectomie boven medicamenteuze behandeling, zeker bij (biologisch) jonge patiënten. Dit zou idealiter nog moeten worden bevestigd in prospectieve studies met lange termijn follow-up waarbij patiënten gerandomiseerd worden tussen adrenalectomie en MR blokkade. Daarnaast zullen toekomstige studies de effectiviteit moeten evalueren van renine-geleide MR blokkade en deze vergelijken met de effectiviteit van adrenalectomie.

Factoren die bij de individuele patiënt in ogenschouw genomen moeten worden met betrekking tot de behandelbeslissing zijn leeftijd, comorbiditeit en operatierisico, respons op hypertensie behandeling voor operatie (aantal antihypertensiva en effectiviteit) en de wens van de patiënt.

Behandel bij voorkeur patiënten met unilateraal primair hyperaldosteronisme (m. Conn) met adrenalectomie. Factoren die bij de individuele patiënt meegenomen moeten worden met betrekking tot de behandelbeslissing (samen beslissen) zijn:

- Biologische leeftijd (in combinatie met comorbiditeit)
- Comorbiditeit
- Operatierisico
- Respons op hypertensie behandeling voor operatie
- Bijwerkingen van medicatie
- Follow-up duur
- Wens van de patiënt

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Evidence tables

Evidence table for systematic review of RCTs and observational studies

Research question: What are the effects of surgery versus medication in patients with primary hyperaldosteronism?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Satoh, 2019	SR and meta-analysis of RCTs, prospective cohort studies and retrospective cohort studies *Literature search up to august 2017* **A:** Catena, 2008 **B:** Wu, 2016 **C:** Kunzel, 2012 **D:** Giacchetti, 2007 **E:** Catena, 2007 **F:** Rossi, 2013 **G:** Indra, 2015 **H:** Wu, 2011 **I:** Catena, 2012 **J:** Fourkiotis, 2013 **K:** Iwakura, 2014 **L:** Holaj, 2015 **M:** Park, 2017 **N:** Sechi, 2009 **O:** Ahmed, 2011 **P:** Mulatero, 2013 <u>Study design</u>:	Inclusion criteria SR: - Comparing operative treatment with medical treatment - Study had to provide values (mean + SD) of at least one of the following variables: Left Ventricular (LV) Mass, serum potassium, systolic blood pressure (SBP), glomerular filtration ratio (GFR), number of oral antihypertensive agents or incidence of cardiovascular events - Articles published after 1985 - English articles - Studies in humans	Describe intervention: **A**: Adrenalectomy **B**: Adrenalectomy **C**: Adrenalectomy **D**: Adrenalectomy in patients with aldosterone-producing adenoma (APA) **E**: Unilateral adrenalectomy **F**: Adrenalectomy **G**: Adrenalectomy in patients with APA **H**: Adrenalectomy **I:** Adrenalectomy **J:** Unilateral adrenalectomy **K:** Patients with unilateral disease underwent laparoscopic adrenalectomy **L:** Patients with unilateral APA underwent adrenalectomy	Describe control: **A**: Treatment with spironolactone (100mg/day) **B**: Mineralcorticoid Receptor Antagonist (MRA) treatment **C**: MRA treatment **D**: Pharmalogical treatment of idiopathic hyperaldosteronism **E**: Spironolactone (50-300mg/day; average dose 121 mg/day) **F**: Mineralcorticoid receptor (MR) antagonist **G**: Spironolactone (50mg/day) **H**: Spironolactone (50mg/day) **I:** Spironolactone (50-300mg/day; average dose 121 mg/day)	<u>Duration of follow-up[a]</u>: **A:** 7.4 years (mean) **B**: 5.75 years (mean) **C**: 4.3 years (mean) **D**: 34.4 months (mean) **E**: 6.4 years (mean) **F**: 36.0 months (median)[a] **G**: 12 months **H**: 12 months **I:** 6.4 years (mean) **J:** 12 months **K:** 12 months **L:** 6 years **M:** Surgical: 3.8 years; Medical: 4.6 years **N:** 12 months **O:** 6 months **P:** 12 years (median) <u>For how many participants were no complete outcome data available?</u> (intervention/control) Not reported in SR	<u>Outcome measure-1: Systolic blood pressure</u> Effect measure: MD (95% CI) **D**: -5.00 (-13.92-3.92) **F**: -6.00 (-11.59- -0.41) **H**: -2.60 (-10.38-5.18) **I:** -2.00 (-7.50-3.50) **J:** 4.00 (0.19-7.81) **K**: -5.00 (-9.44- -0.56) **L:** 1.00 (-10.19-12.19) **M**: 2.70 (-11.40-16.80) Pooled effect (random effects model): MD: -1.88 (95% CI -5.16 to 1.39) favoring adrenalectomy Heterogeneity (I^2): 50% <u>Outcome measure-2: Cardiovascular events</u> Effect measure: RR (95% CI): **A**: 1.03 (0.36-2.98) **B:** 0.88 (0.72-1.06) **C:** 0.21 (0.05-0.89) **P:** 2.80 (0.65-12.17)	<u>Facultative</u>: Brief description of author's conclusion: Results indicate that surgery is associated with a reduced need for additional antihypertensive drugs than MR antagonist treatment in patients with PA. Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question: Due to heterogeneity within studies which compared adrenalectomy in APA patients and MR antagonist treatment in IHA patients, the comparison is not correct and therefore outcomes are not suitable for all PA patients.

	A: Prospective clinical trial **B**: Retrospective study **C**: Cross-sectional study **D**: Prospective clinical trial **E:** Prospective clinical trial **F:** Prospective trial **G**: Prospective clinical trial **H**: Prospective study **I:** Prospective study **J:** Prospective cohort study **K:** Prospective study **L:** Prospective study **M:** Retrospective study **N:** Prospective study **O:** Cohort study **P**: Retrospective cohort study <u>Setting and Country</u>: **A**: Italy **B**: Taiwan **C**: Germany **D**: Italy **E**: Italy **F**: Italy **G**: Czech republic **H**: Taiwan **I:** Italy **J:** Germany **K:** Japan **L:** Czech republic **M:** South Korea **N:** Italy **O:** Australia **P**: Italy	Exclusion criteria SR: - Not specifically reported *16 studies included* <u>Important patient characteristics at baseline</u>: <u>*N, mean age*[a]</u> **A**: 377 patients, 53 years **B**: 822 patients, 47 years **C**: 105 patients, 61 years **D**: 61 patients, 51 years **E**: 54 patients, 53 years **F**: 180 patients, 51 years **G**: 31 patients, 50 years **H**: 100 patients, 42 years **I:** 54 patients, 53 years **J:** 29 patients, 49 years **K:** 212 patients, 54 years **L:** 42 patients, 51 years **M:** 48 patients, 60 years **N:** 54 patients, 53 years	**M:** Adrenalectomy **N:** Adrenalectomy **O:** Adrenalectomy **P:** Patients with aldosterone producing adenoma underwent adrenalectomy within 3 months from the Adrenal Vein Sampling (AVS) diagnosis.	**J:** Spironolactone, eplerone or other antihypertensives **K:** MR antagonists **L:** Spironolactone **M:** MRA treatment **N:** Spironolactone (starting 100mg/day; average dose 121mg/day) **O:** Medical treatment with spironolactone (47%) or amiloride (43%) or both (10%) **P:** For patients with bilateral adrenal hyperplasia medical, MRA therapy was initiated immediately after subtype diagnosis. Dose was targeted to obtain normal potassium and BP levels in absence of side effects.		Pooled effect (random effects model): RR: 0.87 (95% CI 0.44 to 1.72) favoring adrenalectomy Heterogeneity (I^2): 52% <u>Outcome measure-3: Number of antihypertensive agents</u> Effect measure: MD (95% CI) **F:** -0.97 (-1.36- -0.58) **O:** -2.37 (-2.70- -2.04) **L**: -1.50 (-2.45- -0.55) Pooled effect (random effects model): MD: -1.62 (95% CI -2.67 to -0.58) favoring adrenalectomy Heterogeneity (I^2): 93% <u>Outcome measure-4: Hypokalemia</u> Effect measure: MD (95% CI) **C:** 0.10 (-0.06-0.26) **F**: 0.12 (-0.01-0.25) **H:** -0.16 (-0.32-0.00) **L**: 0.00 (-0.21-0.21) **M**: 0.52 (0.21-0.83) Pooled effect (random effects model): MD: 0.09 (95% CI -0.08 to 0.25) favoring medication Heterogeneity (I^2): 77%	Sensitivity analyses (excluding small studies; excluding studies with short follow-up; excluding low quality studies; relevant subgroup-analyses); mention only analyses which are of potential importance to the research question Heterogeneity: Clinical heterogeneity due to subgroups within PA: APA and IHA: This review combined articles on APA treated with adrenalectomy and IHA treated with MR antagonist.

	Source of funding and conflicts of interest: Not reported for individual studies. The authors of the SR declare that they have no conflict of interest.	**O:** 41 patients, age not reported **P:** 270 patients, 44 years *Sex[a]:* **A**: 68% Male **B**: 44% Male **C**: 64% Male **D**: 60% Male **E**: 70% Male **F**: 57% male **G**: 64% male **H**: 42% male **I:** 70% male **J:** 59% male **K:** 42% male **L:** 57% male **M:** Not reported for subgroup **N:** 70% male **O:** Not reported for subgroup **P:** 60% male No information on comparability of groups at baseline					
Velema, 2018	Type of study: Post hoc comparative effectiveness study within the Subtyping Primary Aldosteronism: A Randomized Trail Comparing Adrenal Vein Sampling and Computed Tomography Scan (SPARTACUS) trial	Inclusion criteria: - Legally capacitated - Age 18 years or older - Diagnosed with hypertension that is difficult to treat, or accompanied by hypokalemia, either spontaneous or induced by use of diuretics	Describe intervention: Adrenalectomy	Describe control: Mineralocorticoid Receptor Antagonist (MRA) based treatment	Length of follow-up: 1 year Incomplete outcome data: No incomplete outcome data Loss-to-follow-up: No loss-to-follow-up	Outcome measures and effect size (include 95%CI and p-value if available): Quality of life, SF-36 scores mean difference with reference population: Physical functioning, mean (95%CI): I: 2.5 (0.7-4.3) C: -0.4 (-2.8-2.0)	*Authors conclusion:* In conclusion, QoL in PA is better 1 year after ADX than 1 year after initiation of MRAs. However, both treatment modalities improve QoL, which is relevantly impaired before treatment compared with the general population. Our findings underscore the need to identify patients with PA and support the practice to

	Funding and conflicts of interest: The original SPARTACUS trial was supported by a grant from ZonMW Doelmatigheids Onderzoek 2010-2012 E&K (171002102) and by a grant from the Institute of Cardiology, Warsaw, Poland. The authors did not report conflict of interest	- Positive result on sodium loading test, i.e. insufficient suppression of aldosterone - Cooperating patients and willing to give written informed consent <u>Exclusion criteria</u>: - Unsuitability for or objection to undergo AVS, CT or adrenal surgery - Pregnant - Glucocorticoid remediable aldosteronism or adrenal carcinoma - Severe or terminal co-morbidity with seriously interferes with possible treatment or HRQOL. - Requirement of certain medication that interacts with the prescribed treatments <u>N total at baseline</u>: Intervention: 92 Control: 92 <u>Important prognostic factors</u>[2]: *Mean age in years (SD):* *I: 51.8 (10.1)* *C: 54.4 (8.8)*				Role physical, mean (95%C(): I: 1.1 (-1.0-3.2) C: -0.2 (-2.6-2.2) Bodily pain, mean (95%CI): I: 4.0 (2.1-5.9) C: 1.3 (-0.9-3.4) General health, mean (95%CI): I: 0.8 (-1.4-3.0) C: -4.4 (-6.6 – -2.2) Vitality, mean (95%CI): I: -0.8 (-3.0-1.3) C: -6.1 (-8.1 – -4.1) Social functioning, mean (95%CI): I: 0.2 (-2.0-2.4) C: -3.0 (-5.6 – -0.5) Role emotional, mean (95%CI): I: 0.7 (-1.6-2.9) C: -0.7 (-3.0-1.7) Mental health, mean (95%CI): I: 0.8 (-1.4-3.1) C: -3.7 (-5.8 – -1.5) Physical component summary (PCS), mean (95%CI): I: 2.4 (0.3-4.5) C: -1.5 (-4.0-0.9) Mental component summary (MCS), mean (95%CI):	select patients who are amenable for ADX. Adrenalectomy treatment for unilateral adrenal enlargement or unilateral aldosterone hypersecretion with contralateral aldosterone suppression was demonstrated. All other patients received MRA based treatment. All patients were further treated with conventional antihypertensive drugs according to a treatment algorithm targeting a blood pressure of <135/85 mmHg using semiautomatic device. Study population are patients with hypertension, without adrenal carcinoma or remediable aldosteronism

		Male sex: *I: N=66 (71.7%)* *C: N=78 (84.8%)* *Median Body Mass Index in kg/m²* *(IQR):* *I: 27.5 (25.2-30.5)* *C: 29.4 (26.7-32.6)* *Mean Serum potassium in mEq/L (SD):* *I: 3.5 (0.5)* *C: 3.6 (0.4)* Groups are not comparable at baseline				I: -0.2 (-2.4 – 2.1) C: -4.0 (-6.3 – -1.8) <u>EQ-5D</u> OR for reporting problems on EQ-5D dimension during follow-up according to generalized estimating equation analysis (Adrenalectomy versus MRA treatment), adjusted OR (95%CI): Mobility: 0.52 (0.23-1.20) Self-care: 0.14 (0.01-2.50) Usual activities: 0.35 (0.17-0.75) Pain/discomfort: 0.52 (0.30-0.91) Anxiety/depression: 0.79 (0.39-1.60)	
Araujo Castro, 2022	Type of study: Retrospective cohort study Setting and country: SPAIN-ALDO registry, Spain Funding and conflicts of interest: The research was funded by Sociedad Española de Endocrinología y Nutrición (SEEN). The authors declare no conflict of interest	<u>Inclusion criteria</u>: - Patients with PA from the Spanish Primary Aldosteronism Registry of the Spanish Endocrinology and Nutrition Society (SPAIN-ALDO) who had follow-up between 2018 and 2020 - Patients who underwent adrenalectomy or were under medical treatment with MRA - Patients who had clinical, hormonal	Describe intervention: Adrenalectomy	Describe control: Mineralocorticoid Receptor Antagonist (MRA) in monotherapy or in combination with other hypertensive drugs	<u>Length of follow-up</u>: 2 years <u>Loss-to-follow-up</u>: Loss-to-follow-up or incomplete outcome data were not included in the analysis of the study	Outcome measures and effect size (include 95%CI and p-value if available): Systolic blood pressure, mean between treatment difference in mmHg (SD): I: -19.6 (22.5) C: -17.5 (22.7) MD -2.10 (95%CI -7.7-3.4) Diastolic blood pressure, mean between treatment difference in mmHg (SD): I: -11.8 (14.9) C: -8.6 (15.2) New cardiovascular events I: N=2 (3.9%) C: N=7 (6.4%) HR 0.5 (95%CI 0.1-2.2)	*Authors conclusion:* In patients with PA, MRA and surgery offer a similar cardiovascular, metabolic, and renal protection, in a short-term follow-up, but surgery improves biochemical control and reduces pill burden more commonly than MRA, leading to hypertension cure or improvement in up to 83% of the patients. Short follow-up period. No correction for confounding for all outcomes.

		and biochemical information during follow-up <u>Exclusion criteria</u>: - Patients with confirmed co-secretion of cortisol <u>N total at baseline</u>: Intervention: 100 Control: 168 <u>Important prognostic factors</u>[2]: *Mean age in years (SD):* *I: 52.7 (9.4)* *C: 54.7 (12.5)* *Female sex:* *I: N=54 (54.6%)* *C: N=70 (41.7%)* *Mean Body Mass Index in kg/m² (SD):* *I: 29.1 (6.1)* *C: 30.0 (6.1)* *Hypertension grade ≥2:* *I: N=63 (76.8%)* *C: N=108 (70.6%)* *Type 2 diabetes:* *I: N=15 (15%)* *C: N=33 (19.6%)* Groups are not comparable at baseline				Number of antihypertensive drugs, mean between treatment difference (SD): I: -1.3 (1.3) C: 0.0 (1.4)	For cardiovascular events cox regression was performed but not reported which covariates were included in the analysis. Adrenalectomy treatment for unilateral and bilateral PA

Buffolo, 2020	Type of study: Prospective cohort study Setting and country: QUALITY study, Italy Funding and conflicts of interest:	Inclusion criteria: - Patients in the QUALIty of Life study in Torino, Italy between 2017 and 2019 - Patients with primary aldosteronism (PA) confirmed by diagnosis according to the Endocrine Society guideline and ESH consensus Exclusion criteria: Not reported N total at baseline: Intervention: 37 Control: 30 Important prognostic factors[b]: *Mean age in years (SD): 52 (9)* *Sex, female: N=25 (35.7%)* *Mean Body Mass Index in kg/m²: 25.9 (4.1)* *Type 2 diabetes: N=67 (95.7%)* *Presence of comorbidity by CCI: N= 9 (12.8%)*	Describe intervention: Patients with unilateral PA underwent laparoscopic adrenalectomy	Describe control: Treatment with Mineralocorticoid Receptor Antagonist (MRA): Spironolactone (N=14) and potassium canrenoate (N=16)	Length of follow-up: 6 months Incomplete outcome data: Intervention: N=0 (0%) Control: N=3 (10%) Reasons: No MRA medical treatment Loss-to-follow-up: Intervention: N=1(2.7%) Reasons: Not reported Control: N=1 (3%) Reasons: Not reported Incomplete outcome data: No incomplete outcome data reported	Outcome measures and effect size (include 95%CI and p-value if available): Systolic blood pressure, mean in mmHg (SD): I: 121 (11) C: 131 (13) MD -10.00 (95%CI -15.85- -4.15) Diastolic blood pressure, mean in mmHg (SD): I: 78 (8) C: 83 (8) MD -5.00 (95%CI -8.85- -1.15) Quality of life, SF-36 scores: Physical functioning, mean (SD): I: 94.4 (9.6) C: 92.2 (9.2) Role limitations due to physical health problems, mean (SD): I: 91.4 (25.1) C: 91.4 (22.4) Role limitations due to emotional problems, mean (SD): I: 91.7 (26.8) C: 81.6 (37.4) Vitality, mean (SD): I: 69.4 (21.1) C: 65.7 (17.9)	Study included patients with primary aldosteronism and matched controls with essential hypertension. Regarding this study and analysis, we only reported outcome data regarding adrenalectomy versus MRA therapy. Patients who underwent laparoscopic adrenalectomy were only patients diagnosed with unilateral PA, MRA treatment was for unilateral (N=6) and bilateral PA (N=24).

		No information on comparability of Groups at baseline				General mental health, mean (SD): I: 77.9 (16.6) C: 79.1 (13.6) Social functioning, mean (SD): I: 87.3 (14.3) C: 78.6 (18.9) Bodily Pain, mean (SD): I: 87.5 (17.9) C: 84.0 (20.0) General health perceptions, mean (SD): I: 70.3 (22.1) C: 63.1 (16.4) Number of antihypertensive drugs, mean daily defined dose: I: 0.94 (1.26) C: 3.44 (1.43)	
Chen, 2021	Type of study: Prospective cohort study Setting and country: Shanghai, China Funding and conflicts of interest: The present study was financially supported by the Shanghai Municipal Commission of Health. Researchers were also	Inclusion criteria: - Patients with hypertension and primary aldosteronism who are surgically or medically treated in inpatient ward - In ward between November 2018 to July 2020 Exclusion criteria: - Patients with other forms of	Describe intervention: Unilateral adrenalectomy	Describe control: Treatment with mineralocortoid receptor antagonist	Length of follow-up: 6 months Loss-to-follow-up: No loss-to-follow-up reported Incomplete outcome data: No incomplete outcome data reported	Outcome measures and effect size (include 95%CI and p-value if available): Systolic blood pressure, mean between treatment difference in mmHg (SD): I: -9.1 (2.0) C: -10.3 (2.4) MD: 1.2 (95%CI 0.11-2.29) Diastolic blood pressure, mean between treatment difference in mmHg (SD): I: -1.7 (1.3)	*Authors conclusion:* Our study demonstrated that the surgical treatment with adrenalectomy had an effect of early regression of cardiac structure and definite improvement of cardiac function, although both surgery and drug treatment significantly reduced blood pressure and normalized serum potassium concentration.

	financially supported by grants from the National Natural Science Foundation of China, Ministry of Science and Technology, Ministry of Health, Beijing, China, and the Shanghai Commissions of Science and Technology, Education and Health.	secondary hypertension, ischemic heart disease, valvular heart disease, cardiomyopathy, pacemaker implantation, atrial fibrillation or suboptimal echocardiographic windows <u>N total at baseline</u>: Intervention: 39 Control: 28 <u>Important prognostic factors</u>[2]: *Mean age in years (SD):* *I: 49.4 (10.2)* *C: 48.8 (11.5)* *Male sex:* *I: N=26 (66.7%)* *C: N=22 (71.4%)* *Mean Body Mass Index in kg/m² (SD):* *I: 25.7 (3.3)* *C: 26.8 (2.4)* *Median plasma Renin activity in ng/ml/h (IQR):* *I: 0.27 (0.14-0.47)* *C: 0.84 (0.31-1.2)* *Mean serum potassium*				C: -3.4 (1.6) MD: 1.7 (95%CI 0.98-2.42)	Intervention group consisted of 33 patients with aldosterone-producing adenoma and 6 with idiopathic hyperaldosteronism. Medication group consisted of 13 patients with bilateral primary aldosteronism and 15 with clinical requirement

		concentration in mmol/L (SD): *I: 3.3 (0.4)* *C: 3.5 (0.4)* Groups were not comparable at baseline					
Haze, 2021	Type of study: Retrospective cohort study Setting and country: Japan Rare/Intractable Adrenal Diseases Study (JRAS) Funding and conflicts of interest: This study was conducted as a part of the JRAS by a Research Grant from the Japan Agency for Medical Research and Development The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.	Inclusion criteria: - Patients aged 20-90 years - Enrolled in JRAS between 2006 and 2019 - PA diagnosed based on the guidelines of the Japan Endocrine Society and Japanese Society of Hypertension - Patients records who included assessments of plasma aldosterone concentration, plasma renin activity and blood pressure before treatment - Patients who underwent adrenalectomy or was initiated on MRA treatment between month 0 and 6 - Patients who had been observed for more than 6	Describe intervention: Adrenalectomy for patients with a lateralized form of primary aldosteronism	Describe control: Treatment with mineralocortoid receptor antagonist (MRA)	Length of follow-up: Median follow-up period in days (IQR): I: 1048 (475-1901) C: 1126 (412-1855) Loss-to-follow-up: No loss-to-follow-up reported Incomplete outcome data: Systolic blood pressure N=247 (12.4%) Diastolic blood pressure N=262 (13.2%) No reason(s) reported	Outcome measures and effect size (include 95%CI and p-value if available): Mean systolic blood pressure in mmHg (SD): I: 129 (15) C: 133 (15) MD: -4.00 (95%CI -5.36- -2.64) Mean diastolic blood pressure in mmHg (SD): I: 82 (11) C: 83 (11) MD: -1.00 (95%CI -2.00 – 0.00)	Primary analysis was association between aldosterone to renin ratio (ARR) and pulse pressure with composite cardiovascular disease events only unadjusted data regarding blood pressure was used for this summary.

		months from baseline Exclusion criteria: Not reported N total at baseline: Intervention: 740 Control: 1247 Important prognostic factors[2]: *Mean age in years (SD):* *I: 51.5 (11.7)* *C: 54.2 (10.5)* *Female sex:* *I: N=368 (49.7%)* *C: N=666 (53.4%)* *Mean Body Mass Index in kg/m² (SD):* *I: 24.2 (4.1)* *C: 25.1 (4.1)* *Mean duration of hypertension in years (SD):* *I: 10.1 (9.1)* *C: 8.0 (8.7)* *History of diabetes:* *I: N=121 (16.4%)* *C: N=182 (14.6%)* Groups are not comparable at baseline					

Katabami, 2019	Type of study: Retrospective cohort study Setting and country: Japan Primary Aldosteronism Study (JPAS) Funding and conflicts of interest: This research was supported by grants-in-aid from the Practical Research Project for Rare/Intractable Diseases, funded by the Japan Agency for Medical Research and Development, AMED, Japan . This study was also supported by a grant from Ministry of Health, Labor, and Welfare, Japan. No conflicts of interested reported.	Inclusion criteria: - Patients enrolled in the JPAS between January 2006 and October 2016 with primary aldosteronism with confirmed unilateral subtype Exclusion criteria: - Bilateral subtype - Unsuccessful adrenal vein sampling (AVS) - AVS without adrenocorticotropic hormone stimulation - Missing follow-up data - Incomplete data on blood pressure and/or antihypertensive drugs - Patients in medically treated group who missed out on receiving MRAs N total at baseline: Intervention: 63 Control: 276 Important prognostic factors[2]: *Median age in years (IQR):* *I: 54.0 (42.4-61.0)*	Describe intervention: Unilateral adrenalectomy	Describe control: Treatment with mineralocortoid receptor antagonist for unilateral PA	Length of follow-up: 6 months Loss-to-follow-up: Patients with missing data were excluded Incomplete outcome data: Patients with incomplete outcome data regarding blood pressure and/or antihypertensive drugs were excluded	Outcome measures and effect size (include 95%CI and p-value if available): Systolic blood pressure, median between treatment difference in mmHg (IQR): I: -9.0 (-22.0 – -3.0) C: -5.0 (-25.0 – 6.0) Diastolic blood pressure, median between treatment difference in mmHg (IQR): I: -4.5 (-12.0 – 7.0) C: -7.0 (-13.0 – 4.0) Serum potassium normalization rate: I: N=50 (90.9%) C: N=55 (100%) Daily defined dose of antihypertensive drugs, median between treatment difference (IQR): I: -1.0 (-1.9 – 0.0) C: 0.5 (-0.1 – 2.0)	*Authors conclusion:* The current study provides further evidence that AdX is the first choice of treatment in the patients with unilateral primary aldosteronism in terms of clinical and biochemical outcome. The superior effects of AdX on hyper-tension and hypokalemia should contribute to a better long- term prognosis in unilateral primary aldosteronism. Only participants with unilateral subtype of PA were included in this study. Only propensity matched score outcomes were used for the analysis regarding the summary (I: N=55, C: N=55).

		C: 60.0 (54.0-64.0) *Female sex:* *I: N=127 (46%)* *C: N=20 (32%)* *Median duration of hypertension in years (IQR):* *I: 9.0 (4.0-17.0)* *C: 12.5 (4.0-20.0)* *Median serum potassium level in mmol/liter (IQR):* *I: 3.4 (3.0-3.7)* *C: 3.5 (3.1-3.8)* *Diabetes mellitus* *I: N=47 (17.3%)* *C: N=13 (20.6%)* Groups are not comparable at baseline					
Meng, 2019	Type of study: Retrospective cohort study Setting and country: Fuwai Hospital, China Funding and conflicts of interest: This work was supported by the National Key Research and Development Plan of China, the CAMS Innovation Fund for Medical Science and the PUMC Youth Fund.	<u>Inclusion criteria</u>: - Patients who were hospitalized at Fuwai hospital from 1 January 2016 to 31 december 2017 - Proven unilateral primary aldosteronism - Undergone successful adrenal vein sampling in Fuwai hospital <u>Exclusion criteria</u>: Not reported	Describe intervention: Total or partial laparoscopic adrenalectomy (decision by experienced urologist). Spironolactone with or without other antihypertensive agents was administered for preoperative blood pressure control.	Describe control: Mineralocortoid receptor antagonist (MRA) treatment started with 60 milligram spironolactone. The dose of spironolactone was reduced when serum potassium level progressively increased or reached >5.0 mmol per liter. Eplerenone, the acknowledged substitute for	<u>Length of follow-up</u>: Mean follow-up in months (SD): I: 22.05 (6.26) C: 20.57 (4.63) <u>Loss-to-follow-up</u>: No loss-to-follow-up reported <u>Incomplete outcome data</u>: No incomplete outcome data reported	Outcome measures and effect size (include 95%CI and p-value if available): Mean systolic blood pressure in mmHg (SD): I: 120.3 (12.99) C: 133.54 (16.60) MD: -13.24 (95%CI -21.37 - -5.11) Mean diastolic blood pressure in mmHg (SD): I: 79.00 (7.62) C: 87.35 (12.36)	*Authors conclusion:* The cure rate of hypertension in patients with AVS-proven unilateral PA who underwent laparoscopic adrenalectomy was higher than that in patients who underwent medical treatment. Only patients with unilateral PA were included in this study

	Authors declare they have no conflict of interest	N total at baseline: Intervention: 21 Control: 30 Important prognostic factors[2]: *Mean age in years (SD):* *I: 44.63 (10.55)* *C: 50.53 (12.45)* *Female sex:* *I: N=12 (57.1%)* *C: N=10 (33.3%)* *Mean Body Mass Index in kg/m² (SD):* *I: 24.21 (3.78)* *C: 26.99 (3.16)* *Mean duration of hypertension in years (SD):* *I: 8.3 (7.46)* *C: 13.60 (12.61)* *Mean serum potassium level in mmol/liter (SD):* *I: 3.24 (0.44)* *C: 3.42 (0.53)* *Diabetes mellitus:* *I: N=5 (16.7%)* *C: N=0 (0%)* Groups are not comparable at baseline		spironolactone is not registered in China.		MD: -8.35 (95%CI -13.84 - -2.86) Mean number of antihypertensive drugs (SD): I: 0.19 (0.51) C: 2.33 (0.78) Hypokalemia: I: N=0 (0%) C: N-4 (13.3%)	

Murck, 2021	Type of study: Retrospective cohort study Setting and country: German Conn Registry Funding and conflicts of interest: This work was supported by the Else Kro¨ner-Fresenius Stiftung in support of the German Conns Registry-Else-Kröner Hyperaldosteronism Registry, the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme and by the Deutsche Forschungsgemeinschaft (DFG). The authors report no conflicts of interest in this work. HM is owner of Murck-Neuroscience LLC and holds a patent in the area of treatment refractory depression.	Inclusion criteria: - Patients with newly diagnosed PA Exclusion criteria: Not reported N total at baseline: Intervention: 75 Control: 90 Important prognostic factors[2]: *Female Sex:* *N=82 (39%)* No information on comparability of Groups at baseline	Describe intervention: Adrenalectomy in case of a unilateral tumor	Describe control: Mineralocortoid receptor antagonist (MRA) treatment, mainly spironolactone (25-50 milligram per day) for bilateral hyperplasia of the adrenal gland	Length of follow-up: 1 year Loss-to-follow-up: No loss-to-follow-up regarding blood pressure outcome Incomplete outcome data: No reported.	Outcome measures and effect size (include 95%CI and p-value if available): Mean 24-hour systolic blood pressure in mmHg (SD): I: 136.9 (14.1) C: 135.91 (13.9) MD: 0.99 (95%CI -3.31 – 5.29) Mean 24-hour diastolic blood pressure in mmHg (SD): I: 85.56 (10.2) C: 84.60 (8.3) MD: 0.96 (95%CI -1.91 – 3.84)	Study invested four different groups: Male and female after surgical or medical treatment. Regarding this study and analysis, we only reported outcome data regarding adrenalectomy versus MRA therapy.
Nakamaru, 2021	Type of study: Retrospective cohort study Setting and country: Japan Primary Aldosteronism Study (JPAS)	Inclusion criteria: - Patients aged between 20 and 90 years with PA - Underwent adrenal vein sampling (AVS)	Describe intervention: Adrenalectomy	Describe control: Mineralocortoid receptor antagonist (MRA) treatment	Length of follow-up: 36 months Loss-to-follow-up: Not reported Incomplete outcome data:	Outcome measures and effect size (include 95%CI and p-value if available): Number of cardiovascular events: I: N=12 (2%) C: N=11 (4.9%)	Study stratified data according to age (< 65 years versus ≥ 65 years) therefore not all baseline data was available regarding the scope of this summary.

	Funding and conflicts of interest: This study was supported in part by grants-in-aid for the Japan Primary Aldosteronism Study and the Japan Rare Adrenal Diseases Study from the Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development and grants from the National Center for Global Health and Medicine, Japan. The authors declared no competing interests.	Exclusion criteria: - No follow-up data regarding blood pressure or estimated glomerular filtration rate N total at baseline: Intervention: 622 Control: 233 Important prognostic factors[2]: *Female sex:* *I: N=300 (45%)* *C: N=98 (42%)* No information on comparability of Groups at baseline			Regarding outcome number of cardiovascular events: I: N=33 (5.3%) C: N=10 (4.3%) Regarding outcome hyperkalemia: I: N=14 (2.3%) C: N=2 (0.8%) No reason(s) reported	Hyperkalemia I: N=43 (7%) C: N=4 (1.7%)	
Puar, 2020	Type of study: Retrospective cohort study Setting and country: Two referral centres, Singapore Funding and conflicts of interest: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector. TH Puar was supported by the Singapore National	Inclusion criteria: - Patients with PA fulfilling diagnostic criteria recommended by the Endocrine Society guidelines - Managed at referral centre between 2000 and 2019 - Confirmed unilateral PA by adrenal vein sampling - Likely unilateral PA by clinical	Describe intervention: Unilateral adrenalectomy	Describe control: Mineralocortoid receptor antagonist (MRA) treatment with spironolactone, eplerenone or amiloride	Length of follow-up: Mean duration of follow-up (SD): 5.7 years (4.5) Loss-to-follow-up: Not reported Incomplete outcome data: N=12 from MRA treatment group classified in surgery group Reason(s): Opting for surgery in view of medication side effects or patient preference	Outcome measures and effect size (include 95%CI and p-value if available): Mean systolic blood pressure in mmHg (SD): I: 134.4 (14.1) C: 140.0 (19.2) Mean change in systolic blood pressure in mmHg (SD): I: -17.3 (20.3) C: 12.1 (22.5) Mean diastolic blood pressure in mmHg (SD): I: 81.5 (9.2)	*Authors conclusion:* We demonstrated that in patients with confirmed or likely unilateral PA, who are averse to surgery and are tolerant of medications, medical therapy may provide a viable treatment option. Medical therapy improves BP and biochemical control and may offer similar cardiovascular protection. This underscores the importance of diagnosing PA and instituting targeted therapy with MR antagonists. Surgery

	Medical Research Council Research Training Fellowship award. RS Foo was supported by Singapore National Medical Research Council and A*Star Biomedical Research Council.	prediction score (APR) <u>Exclusion criteria</u>: - Patients without adequate follow-up for at least six months post-treatment - Patients with baseline estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73m^2 <u>N total at baseline</u>: Intervention: 86 Control: 68 <u>Important prognostic factors</u>[2]: *Mean age in years (SD):* *I: 51.0 (10.1)* *C: 55.0 (9.1)* *Female sex:* *I: N=37 (43.0%)* *C: N=22 (32.4%)* *Mean Body Mass Index in kg/m^2 (SD):* *I: 26.1 (4.5)* *C: 26.0 (3.8)* *Median duration of hypertension in years (IQR):* *I: 7 (3-11)* *C: 8 (5-10)*				C: 83.3 (11.4) Mean change in diastolic blood pressure in mmHg (SD): I: -6.8 (12.1) C: -2.9 (12.2) Composite cardiovascular events: HR 0.93 (95%CI 0.32-2.67) Median number of anti-hypertensive drugs (IQR): I: 2.0 (1.0-3.0) C: 1.0 (0.0-2.0) Median change in anti-hypertensive drugs (IQR): I: -1.0 (-2.0-0.0) C: 0.0 (-1.0-1.0)	should be the first-line treatment for unilateral PA as it re- duces pill burden and offers the opportunity for cure of hypertension altogether. Patients with (likely) confirmed unilateral PA

		Mean estimated glomerular filtration rate in ml/min per 1.73m^2 *(SD):* *I: 90.7 (19.4)* *C: 83.8 (18.2)* *Diabetes mellitus:* *I: N=19 (22.1%)* *C: N=23 (33.8%)* Groups are not comparable at baseline					
Tan, 2021	Type of study: Prospective cohort study Setting and country: Changi General Hospital Funding and conflicts of interest: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector. The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported	<u>Inclusion criteria</u>: - Patients of age 18 years or older - Confirmed diagnosis of PA in accordance with the 2016 Endocrine Society Guidelines - Completion of baseline questionnaires <u>Exclusion criteria</u>: - Patients with adrenal carcinoma, severe or terminal co-morbidity that interfered with possible treatment or HRQoL or glucocorticoid-remediable aldosteronism <u>N total at baseline</u>: Intervention: 21 Control: 13	Describe intervention: Unilateral adrenalectomy via a minimally invasive transabdominal laparoscopic approach.	Describe control: Medical therapy	<u>Length of follow-up</u>: 1 year <u>Loss-to-follow-up</u>: Not reported <u>Incomplete outcome data</u>: SF-36 I: N=0 C: N=1 (9.1%) EQ-5D I: N=1 (4.7%) C: N=1 (7.7%) Reason(s): Not reported	Outcome measures and effect size (include 95%CI and p-value if available): <u>Quality of life, SF-36 scores:</u> Physical functioning, mean (SD): I: 91.4 (12.5) C: 86.0 (18.7) MD 5.40 (95%CI -7.55 – 18.35) Role physical, mean (SD): I: 94.4 (16.2) C: 77.5 (38.1) MD 16.90 (95%CI -7.87-41.67) Bodily pain, mean (SD): I: 90.6 (12.3) C: 89.3 (18.6) MD 1.30 (-11.55-14.15) General health, mean (SD): I: 75.8 (11.9) C: 66.5 (21.2)	*Authors conclusion:* In conclusion, we found an improvement in HRQoL and depressive symptoms in patients with PA after surgical and medical treatment, with better outcomes observed after surgery. No specific description of medical therapy.

		Important prognostic factors[2]: *Mean age in years (SD):* *I: 48.1 (11.4)* *C: 56.4 (9.6)* *Female sex:* *I: N=8 (38.1%)* *C: N=2 (15.4%)* *Mean Body Mass Index in kg/m² (SD):* *I: 26.9 (5.3)* *C: 28.6 (5.6)* *Median duration of hypertension in years (IQR):* *I: 8.0 (0-23.0)* *C: 20.0 (3.0-37.0)* *Mean estimated glomerular filtration rate in ml/min per* 1.73m² *(SD):* *I: 88.45 (20.3)* *C: 88.8 (16.9)* *Diabetes mellitus:* *I: N=7 (33.3%)* *C: N=5 (38.5%)* Groups are not comparable at baseline				MD 9.30 (95%CI -4.94-23.54) Vitality, mean (SD): I: 75.3 (10.8) C: 69.5 (25.9) MD 5.80 (95%CI -11.01-22.61) Social functioning, mean (SD): I: 91.0 (14.1) C: 87.5 (16.7) MD 3.50 (95%CI -8.73-15.73) Role emotional, mean (SD): I: 94.4 (17.2) C: 93.3 (21.1) MD 1.10 (95%CI -14.20-16.40) Mental health, mean (SD): I: 84.4 (14.8) C: 83.2 (14.9) MD 1.20 (95%CI -10.29-12.69) EQ-5D index score, median (IQR): I: 1.00 (1.00-1.00) C: 1.0 (0.838-1.0)	
Wada, 2017	Type of study: Retrospective cohort study	Inclusion criteria: - Patients with PA who underwent adrenal vein	Describe intervention: Unilateral adrenalectomy	Describe control: Mineralocortoid Receptor Antagonist (MRA) treatment	Length of follow-up: 6 months Loss-to-follow-up:	Outcome measures and effect size (include 95%CI and p-value if available):	*Authors conclusion:* the potential occurrence of hyperkalemia should be considered after medical

	Setting and country: West Japan Adrenal Vein Sampling study (WAVES-J), Japan Funding and conflicts of interest: This study was supported in part by grants-in-aid for the study of primary aldosteronism in Japan (JPAS), including a Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development and a Grant for National Center for Global Health and Medicine.	sampling from January 2006 to December 2013. - Diagnosis of PA was established by at least one positive result of confirmatory testing. - Patients who had at least one of the recordings of the data after the treatment <u>Exclusion criteria</u>: - Patients who did not take MRA's after diagnosis of PA <u>N total at baseline</u>: Intervention: 142 Control: 234 <u>Important prognostic factors</u>[2]: *Mean age in years (SD):* *I: 53 (11)* *C: 55 (12)* *Female sex:* *I: N=71 (50%)* *C: N=136 (58%)* *Mean duration of hypertension in years (SD):* *I: 9 (8)* *C: 8 (8)*			Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) <u>Incomplete outcome data</u>: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)	Mean systolic blood pressure in mmHg (SD): I: 128.99 (14.0) C: 130.81 (14.0) MD -1.82 (95%CI -4.74-1.10) Mean diastolic blood pressure in mmHg (SD): I: 79.51 (11.2) C: 80.73 (11.0) MD -1.22 (95%CI -3.54-1.09) Mean number of anti-hypertensive drugs (SD): I: 1.1 (1.1) C: 1.9 (0.8) MD -0.83 (95%CI -1.03- -0.63) Hyperkalemia I: N=14 (9.8%) C: N=9 (3.8%)	treatment as well as surgical treatment for PA, especially in patients with older age (460 years) and impaired renal function (eGFR < 70 ml min^{-1} per 1.73 m^2). No specific description of medical therapy. Data is stratified according to presence or absence of hyperkalemia (serum potassium > 5 mEq l^{-1}).

		Median aldosterone renin ratio (IQR): *I: 1085 (482-2101)* *C: 420 (275-695)* *Mean serum potassium in m Eq l^{-1} (SD):* *I: 3.3. (0.6)* *C: 3.8 (0.4)* Groups are not comparable at baseline					
Zavatta, 2019	Type of study: Prospective cohort study Setting and country: Endocrinology unit of the S. Orsola-Malpighi University Hospital of Bologna, Italy Funding and conflicts of interest: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector. The authors declare that they have no conflict of interest.	Inclusion criteria: - Patients diagnosed with PA according to current guidelines Exclusion criteria: - Patients diagnosed with pheochromocytoma - Patients with known aortic bicuspid valve or connective tissue disorders N total at baseline: Intervention: 12 Control: 33 Important prognostic factors[2]: No information on comparability of Groups at baseline	Describe intervention: Unilateral adrenalectomy	Describe control: Treatment with aldosterone antagonist (canrenone) with a mean dosage of 61,5 milligram (SD 31.4)	Length of follow-up: I: 1.5 years C: 3.5 years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Mean number of antihypertensive drugs (SD): I: 1.8 (1.7) C: 2.3 (1.3)	Study compared PA with essential hypertension. Therefore, no baseline data of the intervention and control group within patients with PA, were available.
[a]; Results are extracted from individual studies; [b] no prognostic factors available for subgroups, only for general PA patients							

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

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

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Satoh, 2019	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes

1. Research question (PICO) and inclusion criteria should be appropriate and predefined
2. Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched
3. Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons
4. Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported
5. Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)
6. Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)
7. Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I^2)?
8. An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
9. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a “yes,” source of funding or support must be indicated for the systematic review AND for each of the included studies.

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

Author, year	Selection of participants Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes, probably yes, probably no, definitely no	Exposure Can we be confident in the assessment of exposure? Definitely yes, probably yes, probably no, definitely no	Outcome of interest Can we be confident that the outcome of interest was not present at start of study? Definitely yes, probably yes, probably no, definitely no	Confounding-assessment Can we be confident in the assessment of confounding factors? Definitely yes, probably yes, probably no, definitely no	Confounding-analysis Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables? Definitely yes, probably yes, probably no, definitely no	Assessment of outcome Can we be confident in the assessment of outcome? Definitely yes, probably yes, probably no, definitely no	Follow up Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed? Definitely yes, probably yes, probably no, definitely no	Co-interventions Were co-interventions similar between groups? Definitely yes, probably yes, probably no, definitely no	Overall Risk of bias Low, Some concerns, High
Araujo Castro, 2022	*Definitely yes* Reason: Participants were selected from a registry using clear inclusion and exclusion criteria	*Probably yes* Reason: Exposure is surgery or medication, data from records	*Probably yes* Reason: Outcome data was measured pre- and post-intervention, regarding	*Probably yes* Reason: Possible confounding factors were reported	*Definitely no* Reason: No adjustment for confounding factors in analysis	*Probably yes* Reason: Clear definition of outcome, data from records. Regarding cardiovascular event no exact definition	***Probably no*** Reason: Follow-up was too short for the outcome cardiovascular events, for other outcomes it could be sufficient	*No information*	**High (regarding confounding analysis, assessment of outcome and follow-up #cardiovascular events)** **Some concerns (regarding confounding analysis #bloodpressure and number of**

									antihypertensive drugs)
Buffolo, 2020	*Definitely no* Reason: Participants for the surgical treatment were differently selected then participants for the medical treatment	*Definitely yes* Reason: Exposure is surgery or medication	*Probably yes* Reason: Before screening tests all interfering antihypertensive drugs were stopped and outcomes were measured pre- and post intervention	*Definitely no* Reason: Possible confounding factors were reported	*Definitely no* Reason: No adjustment for confounding factors in analysis	*Probably yes* Reason: Regarding QoL standardized questionnaire was used	*Probably yes* Reason: Follow-up was sufficient for outcomes	*No information*	**High (regarding selection bias and confounding analysis)**
Chen, 2021	*Probably yes* Reason: Participants were prospectively selected with in- and exclusion criteria	*Definitely yes* Reason: Exposure is surgery or medication	*Probably yes* Reason: Outcome data were measured pre- and post intervention with clear definition and instruction	*Probably yes* Reason: Possible confounding factors were reported	*Definitely no* Reason: No adjustment for confounding factors in analysis	*Probably yes* Reason: Clear definitions and protocols for measuring outcomes	*Probably yes* Reason: Follow-up was six months, sufficient for outcome blood pressure	*No information*	**Some concerns (regarding confounding analysis because groups were not comparable at baseline)**
Haze, 2021	*Probably yes* Reason: Participants were retrospectively selected from registry with clear in- and exclusion criteria	*Definitely yes* Reason: Exposure is surgery or medication, data is from records	*Probably yes* Reason: Outcome data were measured pre- and post intervention	*Definitely yes* Reason: Possible confounding factors were reported	*Probably no* Reason: Regarding analysis for outcome blood pressure there was no	*Probably yes* Reason: Clear definition and protocol for measuring outcome	*Probably yes* Reason: Follow-up was six months, sufficient for outcome blood pressure	*No information*	**Some concerns (regarding confounding analysis because groups were not comparable at baseline)**

					adjustment for confounders				
Katabami, 2019	*Definitely yes* Reason: Participants were retrospectively selected from registry with clear in- and exclusion criteria	*Definitely yes* Reason: Exposure is surgery or medication, data is from records	*Probably yes* Reason: Outcome data were measured pre- and post-intervention	*Definitely yes / Probably yes / Probably no / Definitely no* Reason: Confouding factors were reported	*Definitely yes* Reason: Propensity score matching was used to correct for confounding variables	*Probably no* Reason: No clear definition for outcome #normalization of serum potassium levels	*Definetly yes* Reason: Follow-up was six months, sufficient for outcome blood pressure, normokalemia and antihypertensive drugs and missing data were imputed	*No information*	**Some concerns (regarding outcome measurement #normokalemia)** **Low (#blood pressure and number of antihypertensive drugs)**
Meng, 2019	*Probably yes* Reason: Participants were retrospectively selected from registry with clear inclusion criteria	*Definitely yes* Reason: Exposure is surgery or medication, data is from medical records	*Probably yes* Reason: Outcome data were measured pre- and post-intervention	*Probably yes* Reason: Confouding factors were reported	*Definitely no* Reason: No adjustment for confounding factors in analysis	*Probably no* Reason: No clear definition for outcome #hypokalemia, clear definition and protocol for measuring other outcomes	*Probably yes* Reason: Follow-up was sufficient for outcomes, no missing data	*No information*	**Some concerns (regarding confounding analysis and outcome assessment)**
Murck, 2021	*Probably no* Reason: Subgroup of participants (newly diagnosed) were selected from registry with	*Probably yes* Reason: Exposure is surgery or medication,	*Probably yes* Reason: Outcome data were measured pre- and post-intervention	*Probably no* Reason: Not all confounding factors were reported	*Definitely no* Reason: No adjustment for confounding factors in analysis	*Probably yes* Reason: Clear protocol for measuring outcome data	*Probably yes* Reason: Follow-up was sufficient for outcome	*No information*	**High (Regarding selection bias, confounding assessment and analysis)**

	no clear in- and exclusion criteria	data is from medical records							
Nakamaru, 2021	*Probably yes* Reason: Patients were selected from JPAS registry with in- and exclusion criteria	*Probably yes* Reason: Exposure is surgery or medication, data is from medical records	*Probably yes* Reason: Outcome data were measured pre- and post-intervention	*Probably no* Reason: Not all confounding factors were reported because of stratification of data	*Definitely no* Reason: No adjustment for confounding factors in analysis regarding outcomes cardiovascular events or hyperkalemia	*Probably yes* Reason: Clear protocol for measuring outcome data	*Probably yes* Reason: Follow-up was sufficient for outcomes	*No information*	**Some concerns (regarding confounding assessment and analysis)**
Puar, 2020	*Probably no* Reason: Proportion of patients were selected according to primary aldosteronism prediction score	*Probably yes* Reason: Exposure is sugery or medication, data is from medical records	*Probably yes* Reason: Outcome data were measured pre- and post-intervention	*Probably yes /Probably no* Reason: Confounding factors were reported for outcome #cardiovascular events and not for outcome #blood pressure and #number of antihypertensive drugs	*Definitely yes / Definitely no* Reason: Adjustment for confounding factors in analysis regarding outcome #cardiovascular events not for outcome #blood pressure	*Probably yes* Reason: Outcome data was obtained from medical records	*Probably yes* Reason: Follow-up was sufficient for outcomes	*No information*	**Some concerns (regarding selection bias for outcome #cardiovascular events)** **High (regarding selection bias and confounding assessment and analysis for outcome #blood pressure and #number of antihypertensive drugs)**
Tan, 2021	*Probably yes*	*Probably no*	*Probably yes*	*Probably no*	*Definitely no*	*Probably yes*	*Probably yes*	*No information*	**Some concerns (regarding**

	Reason: Patients were prospectively selected with clear in- and exclusion criteria	Reason: No clear definition of exposure of medical therapy (control)	Reason: Outcome data were measured pre- and post-intervention	Reason: Not all confounding factors were reported	Reason: No adjustment for confounding factors in analysis	Reason: Outcome data was measured using standardized questionnaires	Reason: Follow-up was sufficient for outcomes		**assessment of exposure and confounding assessment and analysis)**
Velema, 2019	*Probably yes* Patients were prospectively selected with clear in- and exclusion criteria	*Probably yes* Reason: Clear definition of exposures	*Probably yes* Reason: Outcome data were measured pre- and post-intervention	*Probably yes* Reason: Confounding factors were reported	*Probably yes* Reason: Mixed model analysis was used to compare outcomes before and after the two treatments	*Probably yes* Reason: Outcome data was measured using standardized questionnaires	*Probably yes* Reason: Follow-up was sufficient for outcomes	*Probably yes* Reason: Study reported all patients were further treated with conventional antihypertensive drugs	**Low**
Wada, 2017	*Probably yes* Reason: Patients were selected from WAVES-J study with in- and exclusion criteria	*Probably yes* Reason: Exposure is sugery or medication, data is from medical records	*Probably yes* Reason: Outcome data were measured pre- and post-intervention	*Probably yes* Reason: Confouding factors were reported	*Definitely no* Reason: No adjustment for confounding factors regarding outcomes of interest in analysis	*Probably yes* Reason: Outcome data was measured using a clear definition	*Probably yes* Reason: Follow-up was sufficient for outcomes	*No information*	**Some concerns (regarding confounding analysis)**
Zavatta, 2019	*Probably yes* Reason: Patients were selected prospectively with in- and exclusion criteria	*Probably yes* Reason: Exposure is surgery or medication with clear definitions	*Probably yes* Reason: Outcome data were measured pre- and post-intervention	*Definitely no* Reason: No confounding factors were reported	*Definitely no* Reason: No adjustment for confounding factors regarding outcomes of interest in analysis	*Probably yes* Reason: Outcome data was measured using a clear definition	*Definitely no* Reason: Follow-up for intervention and control group was different, no report of missing data	*No information*	**High (regarding confounding assessment and analysis and follow-up)**

Footnotes
Selection of participants Example of low risk of bias: Exposed and unexposed drawn for same administrative database of patients presenting at same points of care over the same time frame
Exposure Examples of low risk of bias: Secure record (e.g. surgical records, pharmacy records); Repeated interview or other ascertainment asking about current use/exposure
Confounding Examples of low risk of bias regarding assessment: Interview of all participants; Self-completed survey from all participants; Review of charts with reproducibility demonstrated; From database with documentation of accuracy of abstraction of prognostic data.
Example of low risk of bias regarding analysis: Comprehensive matching (e.g. with propensity score) or adjustment for all plausible confounding variables
Assessment of outcome Examples of low risk of bias: Independent blind assessment; Record linkage; For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture
Follow up Examples of low risk of bias: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for
survival data, censoring is unlikely to introduce bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; Missing data have been imputed using appropriated methods
Co-interventions Example of low risk of bias: Most or all relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed

Table of excluded studies

Reference	Reason for exclusion
Chang YH, Chung SD, Wu CH, Chueh JS, Chen L, Lin PC, Lin YH, Huang KH, Wu VC, Chu TS; TAIPAI Study Group. Surgery decreases the long-term incident stroke risk in patients with primary aldosteronism. Surgery. 2020 Feb;167(2):367-377. doi: 10.1016/j.surg.2019.08.017. Epub 2019 Oct 29. PMID: 31676114.	Wrong intervention versus control and no outcome of interest reported
Chen YY, Lin YH, Huang WC, Chueh E, Chen L, Yang SY, Lin PC, Lin LY, Lin YH, Wu VC, Chu TS, Wu KD. Adrenalectomy Improves the Long-Term Risk of End-Stage Renal Disease and Mortality of Primary Aldosteronism. J Endocr Soc. 2019 Mar 25;3(6):1110-1126. doi: 10.1210/js.2019-00019. PMID: 31086833; PMCID: PMC6507624.	No outcome of interest reported
W. Grira, F. Chaker, M. Yazidi, C. Denguir, M. Tebib, M. Chihaoui, H. Slimane, P-158: Long-term evolution of blood pressure and kalemia in patients with primary aldosteronism: surgical treatment versus medical treatment, Annales de Cardiologie et d'Angéiologie, Volume 64, Supplement 1, 2015, Page S76, ISSN 0003-3928,	Article not available in English
Holaj R, Rosa J, Zelinka T, Štrauch B, Petrák O, Indra T, Šomlóová Z, Michalský D, Novák K, Wichterle D, Widimský J Jr. Long-term effect of specific treatment of primary aldosteronism on carotid intima-media thickness. J Hypertens. 2015 Apr;33(4):874-82; discussion 882. doi: 10.1097/HJH.0000000000000464. PMID: 25490707; PMCID: PMC4354456.	Already included in review of Satoh (2019)
Huang WC, Chen YY, Lin YH, Chueh JS. Composite Cardiovascular Outcomes in Patients With Primary Aldosteronism Undergoing Medical Versus Surgical Treatment: A Meta-Analysis. Front Endocrinol (Lausanne). 2021 May 17;12:644260. doi: 10.3389/fendo.2021.644260. PMID: 34079522; PMCID: PMC8165438.	Only meta-analysis for composite outcome
Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Renal Outcomes in Medically and Surgically Treated Primary Aldosteronism. Hypertension. 2018 Sep;72(3):658-666. doi: 10.1161/HYPERTENSIONAHA.118.11568. PMID: 29987110; PMCID: PMC6202119.	No outcome of interest reported
Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Incidence of Atrial Fibrillation and Mineralocorticoid Receptor Activity in Patients With	Wrong intervention versus control

Medically and Surgically Treated Primary Aldosteronism. JAMA Cardiol. 2018 Aug 1;3(8):768-774. doi: 10.1001/jamacardio.2018.2003. PMID: 30027227; PMCID: PMC6143072.	
Jing Y, Liao K, Li R, Yang S, Song Y, He W, Wang K, Yang J, Li Q, Hu J. Cardiovascular events and all-cause mortality in surgically or medically treated primary aldosteronism: A Meta-analysis. J Renin Angiotensin Aldosterone Syst. 2021 Jan-Dec;22(1):14703203211003781. doi: 10.1177/14703203211003781. PMID: 33752505; PMCID: PMC8880484.	Systematic review reported only one outcome of interest
Kwak MK, Lee JY, Kim BJ, Lee SH, Koh JM. Effects of Primary Aldosteronism and Different Therapeutic Modalities on Glucose Metabolism. J Clin Med. 2019 Dec 12;8(12):2194. doi: 10.3390/jcm8122194. PMID: 31842354; PMCID: PMC6947343.	No outcome of interest reported
Lin YF, Peng KY, Chang CH, Hu YH, Wu VC, Chung SD; Taiwan Primary Aldosteronism Investigation (TAIPAI) Study Group. Changes in Glucose Metabolism after Adrenalectomy or Treatment with a Mineralocorticoid Receptor Antagonist for Primary Aldosteronism. Endocrinol Metab (Seoul). 2020 Dec;35(4):838-846. doi: 10.3803/EnM.2020.797. Epub 2020 Dec 2. PMID: 33261310; PMCID: PMC7803597.	No outcome of interest reported
Marzano L, Colussi G, Sechi LA, Catena C. Adrenalectomy is comparable with medical treatment for reduction of left ventricular mass in primary aldosteronism: meta-analysis of long-term studies. Am J Hypertens. 2015 Mar;28(3):312-8. doi: 10.1093/ajh/hpu154. Epub 2014 Oct 21. PMID: 25336498.	No outcome of interest in meta-analysis
Muth A, Ragnarsson O, Johannsson G, Wängberg B. Systematic review of surgery and outcomes in patients with primary aldosteronism. Br J Surg. 2015 Mar;102(4):307-17. doi: 10.1002/bjs.9744. Epub 2015 Jan 20. PMID: 25605481.	No meta-analysis performed because of methodological heterogeneity
Pan CT, Liao CW, Tsai CH, Chen ZW, Chen L, Hung CS, Liu YC, Lin PC, Chang CC, Chang YY, Wu VC, Lin YH; TAIPAI study group †. Influence of Different Treatment Strategies on New-Onset Atrial Fibrillation Among Patients With Primary Aldosteronism: A Nationwide Longitudinal Cohort-Based Study. J Am Heart Assoc. 2020 Mar 3;9(5):e013699. doi:	Wrong intervention versus control

10.1161/JAHA.119.013699. Epub 2020 Feb 19. PMID: 32070205; PMCID: PMC7335564.	
Park KS, Kim JH, Yang YS, Hong AR, Lee DH, Moon MK, Choi SH, Shin CS, Kim SW, Kim SY. Outcomes analysis of surgical and medical treatments for patients with primary aldosteronism. Endocr J. 2017 Jun 29;64(6):623-632. doi: 10.1507/endocrj.EJ16-0530. Epub 2017 Apr 29. PMID: 28458337.	Is already included in review of Satoh (2019)
Rossi GP, Maiolino G, Flego A, Belfiore A, Bernini G, Fabris B, Ferri C, Giacchetti G, Letizia C, Maccario M, Mallamaci F, Muiesan ML, Mannelli M, Negro A, Palumbo G, Parenti G, Rossi E, Mantero F; PAPY Study Investigators. Adrenalectomy Lowers Incident Atrial Fibrillation in Primary Aldosteronism Patients at Long Term. Hypertension. 2018 Apr;71(4):585-591. doi: 10.1161/HYPERTENSIONAHA.117.10596. Epub 2018 Feb 26. PMID: 29483224.	Wrong intervention versus control
Tsai CH, Chen YL, Pan CT, Lin YT, Lee PC, Chiu YW, Liao CW, Chen ZW, Chang CC, Chang YY, Hung CS, Lin YH. New-Onset Atrial Fibrillation in Patients With Primary Aldosteronism Receiving Different Treatment Strategies: Systematic Review and Pooled Analysis of Three Studies. Front Endocrinol (Lausanne). 2021 May 24;12:646933. doi: 10.3389/fendo.2021.646933. PMID: 34108934; PMCID: PMC8181760.	No outcome of interest reported
Velema MS, Terlouw JM, de Nooijer AH, Nijkamp MD, Jacobs N, Deinum J. Psychological Symptoms and Well-Being After Treatment for Primary Aldosteronism. Horm Metab Res. 2018 Aug;50(8):620-626. doi: 10.1055/a-0628-6847. Epub 2018 Jun 12. PMID: 29895075.	No comparison between intervention and control for outcomes of interest
Wu CH, Yang YW, Hung SC, Tsai YC, Hu YH, Lin YH, Chu TS, Wu KD, Wu VC. Effect of Treatment on Body Fluid in Patients with Unilateral Aldosterone Producing Adenoma: Adrenalectomy versus Spironolactone. Sci Rep. 2015 Oct 19;5:15297. doi: 10.1038/srep15297. PMID: 26477337; PMCID: PMC4609981.	No outcome of interest reported

Literature search strategy

Algemene informatie

Richtlijn: NVVH bijniertumoren	
Uitgangsvraag: Wat zijn de voor- en nadelen van chirurgie ten opzichte van medicatie bij patiënten met M. Conn, op de bloeddrukcontrole (inclusief aantal antihypertensiva), normale kaliumwaarden in het bloed (normokalemia), (lange termijn) cardiovasculaire morbiditeit en mortaliteit en kwaliteit van leven	
Database(s): Ovid/Medline, Embase	Datum: 15-2-2022, 14-3-2022
Periode: 2000-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: **14-3-2022** Naar aanleiding van een gevonden SR van Satoh, is gekozen om de observationele studies vanaf 2017 toe te voegen. Daarnaast is een update uitgevoerd voor de SRs en RCTs en is 1 SR toegevoegd. **15-2-2022** Voor deze vraag is gezocht met de volgende elementen: M. Conn EN adrenalectomy 4 van de sleutelartikelen worden gevonden met het studiedesign SR, RCT. De overige sleutelreferenties worden gevonden met het observationele filter, met uitzondering van de richtlijn.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 15 februari 2022 met relevante zoektermen gezocht naar systematische reviews en RCTs over de chirurgische behandeling van M. Conn. De literatuurzoekactie leverde 114 unieke treffers op. Op 14 maart wordt naar aanleiding van de gevonden SR van Satoh, besloten om een update uit te voeren en de observationele studies toe te voegen. Het totaal aantal gevonden unieke treffers is 542.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs 15-2-2022	65	36	67
RCTs 15-2-2022	56	40	47
Observationele studies 14-3-2022	401	264	427
Update SR 14-3-2022	1	1	1
Totaal			542

Zoekstrategie

Embase

14-3-2022

No.	Query	Results
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#24	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR ('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	**12886408**
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#20	#7 OR #8	**109**
#19	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	**9**
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#17	mineralocorticoid AND antagonists AND treatment AND versus AND surgery AND in AND primary AND aldosteronism AND catena	**1**
#16	(8. AND medical OR surgical) AND therapy AND for AND primary AND aldosteronism AND 'post treatment' AND 'follow up' AND as AND a AND surrogate AND measure AND of AND comparative AND outcomes AND kline	**1**
#15	the AND management AND of AND primary AND aldosteronism AND funder AND 2016 AND case AND detection, AND diagnosis, AND treatment:ti NOT 2008	**1**
#14	management AND of AND endocrine AND disease AND guideline AND williams AND aldosteronism AND 2018	**1**

No.	Query	Results
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#12	puar AND 2021 AND aldosteronism AND outcomes:ti	**1**
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#10	outcomes:ti AND after AND adrenalectomy AND for AND unilateral AND primary AND aldosteronism:ti AND lenders AND 2017	**1**
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#7	#4 AND #5	**43**
#6	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	**1874875**
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	**733409**
#4	#3 AND [1-1-2017]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**710**
#3	#1 AND #2	**2962**
#2	'adrenalectomy'/exp OR 'endoscopic surgery'/exp OR 'laparoscopy'/exp OR 'minimally invasive surgery'/exp OR 'adrenal enucleation':ti,ab,kw OR 'adrenalectom*':ti,ab,kw OR 'hemiadrenalectom*':ti,ab,kw OR 'retroperitoneoscopy'/exp OR retroperioneoscop*:ti,ab,kw OR (((adrenal OR 'minimally invasive') NEAR/3 surger*):ti,ab,kw) OR laparoscop*:ti,ab,kw OR endoscopic*:ti,ab,kw	**645497**
#1	'primary hyperaldosteronism'/exp OR 'aldosterone producing adenoma':ti,ab,kw OR 'aldosteronism primary':ti,ab,kw OR 'primary aldosteronism':ti,ab,kw OR 'primary hyperaldosteronism':ti,ab,kw OR ((conn NEAR/3 (morbus OR disease OR syndrome)):ti,ab,kw)	**9501**

No.	Query	Results
#22	#19 NOT #21	5
#21	#19 AND #20	4
#20	#7 OR #8	109
#19	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	9
#18	composite AND cardiovascular AND outcomes AND in AND patients AND with AND primary AND aldost eronism AND undergoing AND medical AND versus AND surgical AND treatment AND huang	1
#17	mineralocorticoid AND antagonists AND treatment AND versus AND surgery AND in AND primary AND aldosteronism AND catena	1

No.	Query	Results
#16	(8. AND medical OR surgical) AND therapy AND for AND primary AND aldosteronism AND 'post treatment' AND 'follow up' AND as AND a AND surrogate AND measure AND of AND comparative AND outcomes AND kline	1
#15	the AND management AND of AND primary AND aldosteronism AND funder AND 2016 AND case AND detection, AND diagnosis, AND treatment:ti NOT 2008	1
#14	management AND of AND endocrine AND disease AND guideline AND williams AND aldosteronism AN D 2018	1
#13	systematic AND review AND the AND clinical AND outcomes AND of AND mineralocorticoid AND recep tor AND antagonist AND treatment AND versus AND adrenalectomy AND in AND patients AND with AN D primary AND aldosteronism AND satoh AND 2019	1
#12	puar AND 2021 AND aldosteronism AND outcomes:ti	1
#11	composite AND cardiovascular AND outcomes AND in AND patients AND with AND primary AND aldost eronism AND undergoing AND medical AND versus AND surgical AND treatment	1
#10	outcomes:ti AND after AND adrenalectomy AND for AND unilateral AND primary AND aldosteronism:ti AND lenders AND 2017	1
#9	. AND quality AND life AND in AND primary AND aldosteronism AND a AND comparative AND effective ness AND study AND of AND adrenalectomy AND medical AND treatment. AND dekkers AND 2018	1
#8	#4 AND #6 RCT	56
#7	#4 AND #5 SR	65
#6	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1874875
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#4	#3 AND [1-1-2000]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1684
#3	#1 AND #2	2962
#2	'adrenalectomy'/exp OR 'endoscopic surgery'/exp OR 'laparoscopy'/exp OR 'minimally invasive surgery'/exp OR 'adrenal enucleation':ti,ab,kw OR 'adrenalectom*':ti,ab,kw OR 'hemiadrenalectom*':ti,ab,kw OR 'retroperitoneoscopy'/exp OR retroperioneoscop*:ti,ab,kw OR (((adrenal OR 'minimally invasive') NEAR/3 surger*):ti,ab,kw) OR laparocop*:ti,ab,kw OR endoscopic*:ti,ab,kw	574911
#1	'primary hyperaldosteronism'/exp OR 'aldosterone producing adenoma':ti,ab,kw OR 'aldosteronism primary':ti,ab,kw OR 'primary aldosteronism':ti,ab,kw OR 'primary hyperaldosteronism':ti,ab,kw OR ((conn NEAR/3 (morbus OR disease OR syndrome)):ti,ab,kw)	9503

Ovid/Medline
14-3-2022

#	Searches	Results
14	13 not 9 not 8	264
13	5 and (11 or 12)	287

12	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5104379
11	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4091551
10	9 not 8	10
9	5 and 7	19
8	5 and 6	24
7	(exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/)	1358363
6	(meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	552308
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	465
4	limit 3 to yr="2017 -Current"	497
3	1 and 2	1845
2	Adrenalectomy/ or exp Laparoscopy/ or Endoscopy/ or Minimally Invasive Surgical Procedures/ or adrenal enucleation.ti,ab,kf. or adrenalectom*.ti,ab,kf. or hemiadrenalectom*.ti,ab,kf. or retroperioneoscop*.ti,ab,kf. or ((adrenal or minimally invasive) adj3 surger*).ti,ab,kf. or laparocop*.ti,ab,kf. or endoscopic*.ti,ab,kf.	357645
1	exp Hyperaldosteronism/ or aldosterone producing adenoma.ti,ab,kf. or aldosteronism primary.ti,ab,kf. or primary aldosteronism.ti,ab,kf. or primary hyperaldosteronism.ti,ab,kf. or (conn adj3 (morbus or disease or syndrome)).ti,ab,kf.	10735

15-2-2022

#	Searches	Results
9	5 and 7 RCT	40
8	5 and 6 SR	36
7	(exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/)	1352557
6	(meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	547875

5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1190
4	limit 3 to yr="2000 -Current"	1265
3	1 and 2	1836
2	Adrenalectomy/ or exp Laparoscopy/ or Endoscopy/ or Minimally Invasive Surgical Procedures/ or adrenal enucleation.ti,ab,kf. or adrenalectom*.ti,ab,kf. or hemiadrenalectom*.ti,ab,kf. or retroperioneoscop*.ti,ab,kf. or ((adrenal or minimally invasive) adj3 surger*).ti,ab,kf. or laparocop*.ti,ab,kf. or endoscopic*.ti,ab,kf.	356286
1	exp Hyperaldosteronism/ or aldosterone producing adenoma.ti,ab,kf. or aldosteronism primary.ti,ab,kf. or primary aldosteronism.ti,ab,kf. or primary hyperaldosteronism.ti,ab,kf. or (conn adj3 (morbus or disease or syndrome)).ti,ab,kf.	10721

Module 4 – Behandeling Cushing

Uitgangsvraag
Wat is de optimale behandeling voor het ACTH-onafhankelijk syndroom van Cushing op basis van bilaterale bijniervergroting?

De uitgangsvraag omvat de volgende deelvragen:
1. Wat is de rol van chirurgie bij patiënten met een ACTH-onafhankelijk syndroom van Cushing op basis van bilaterale bijniervergroting?
2. Indien de patiënt in aanmerking komt voor een chirurgische behandeling, wat heeft dan de voorkeur: het verwijderen van de grootste bijnier of bilaterale extirpatie?

Inleiding
Het endogeen syndroom van Cushing (CS) omvat ACTH-afhankelijke en ACTH-onafhankelijke etiologiën. De laatste is goed voor ongeveer 15-20% van de gevallen en wordt meestal geïnduceerd door unilaterale bijnieradenomen of bijniercarcinomen vergezeld van autonome cortisol secretie. ACTH-onafhankelijk CS wordt soms veroorzaakt door bilaterale bijnierschorslaesies, waaronder unilateraal functioneel adenoom met een contralaterale niet-functionele massa, bilaterale ACTH-onafhankelijke micro- of macronodulaire bijnierhyperplasie (AIMAH) en bilaterale primaire gepigmenteerde nodulaire bijnierschorsziekte (PPNAD). Het bepalen van de aard en functie van bilaterale bijniermassa's is een uitdaging in de klinische praktijk. In enkele studies is een mogelijke rol voor bijniervene sampling onderzocht om de zijde met de hoogste cortisolproductie te bepalen. Bijniervene sampling met dit doel wordt nog niet routinematig toegepast.

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

1: What are the beneficial and harmful effects of surgery compared to medication (steroid synthesis inhibitors) in patients with ACTH-independent Cushing's syndrome on body weight, clinical symptoms, and cardiovascular events?

PICO 1)

P (Patients)	patients with ACTH-independent Cushing's syndrome with bilateral adrenal enlargement
I (Intervention)	adrenalectomy
C (Control)	medication (steroid synthesis inhibitors)
O (Outcomes)	body weight, blood pressure, diabetes, clinical symptoms (fatigue, general malaise, musculoskeletal complaints), osteoporosis, cardiovascular events, cortisol levels, quality of life, mortality

2: What are the beneficial and harmful effects of adrenalectomy of the largest adrenal gland compared to bilateral adrenalectomy in patients with ACTH-independent Cushing's syndrome who are eligible for surgery?

PICO 2)

P (Patients)	patients with ACTH-independent Cushing's syndrome with bilateral adrenal enlargement who are eligible for surgery
I (Intervention)	adrenalectomy of the most affected side (unilateral)
C (Control)	bilateral adrenalectomy

O (Outcomes)	cortisol levels, body weight, blood pressure, diabetes, clinical symptoms (fatigue, general malaise, musculoskeletal complaints), osteoporosis, cardiovascular events, quality of life, mortality

Relevant outcome measures

PICO 1)

The guideline development group considered body weight, clinical symptoms and cardiovascular events as a critical outcome measure for decision making; and blood pressure, diabetes, osteoporosis, cortisol levels, quality of life and mortality as an important outcome measure for decision making.

PICO 2)

The guideline development group considered cortisol levels as a critical outcome measure for decision making; and body weight, blood pressure, diabetes, clinical symptoms, osteoporosis, cardiovascular events, quality of life, mortality as an important outcome measure for decision making.

A priori, the working group did not define the outcome measures listed above.

The working group defined the following differences per outcome as a minimal clinically (patient) important difference:

- Body weight: Absolute difference >5%
- Blood pressure: 10 mmHg
- Diabetes: GRADE standard limits of 25% for dichotomous outcome measures (RR <0.80 or RR >1.25)
- Clinical symptoms
  - Fatigue: A minimal difference of 0.5 points on the Fatigue Severity Scale or a difference of a similar magnitude on other fatigue assessment instruments
  - General malaise: GRADE standard limits of 10% for continuous outcome measures (RR<0.91 or RR>1.1)
  - Musculoskeletal complaints: GRADE standard limits of 10% for continuous outcome measures (RR<0.91 or RR>1.1)
- Osteoporosis: GRADE standard limits of 25% for dichotomous outcome measures (RR <0.80 or RR >1.25)
- Cortisol levels: GRADE standard limits of 10% for continuous outcome measures (RR<0.91 or RR>1.1)
- Cardiovascular events: Absolute difference >5% for lethal complications, or >25% for serious complications
- Quality of life: A minimal difference of 10 points on the CushingQOL questionnaire or a difference of a similar magnitude on other quality of life instruments
- Mortality: Absolute difference >5%

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2010 until 09-01-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 332 hits. Studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICO's;
- The intervention and comparison had to be as defined in the PICO and reported at least one of the outcomes as defined in the PICO's;
- Research type: Systematic review; RCT

- Articles written in English or Dutch

Ten studies were initially selected based on title and abstract screening. After reading the full text, 10 studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included for both PICO's.

Results
No studies were included in the analysis of the literature.

Summary of literature
Description of studies
Not applicable.

Results
Body weight, blood pressure, diabetes, clinical symptoms, osteoporosis, cardiovascular events, cortisol levels, quality of life, mortality
No studies were found that directly compared adrenalectomy with medication in patients with ACTH-independent Cushing's syndrome with bilateral adrenal enlargement on the outcomes: body weight, blood pressure, diabetes, clinical symptoms, osteoporosis, cardiovascular events, cortisol levels, quality of life and mortality (PICO 1).
No studies were found that directly compared adrenalectomy of the most affected side with bilateral adrenalectomy in patients with ACTH-independent Cushing's syndrome with bilateral adrenal enlargement who are eligible for surgery on the outcomes: cortisol levels, body weight, blood pressure, diabetes, clinical symptoms, osteoporosis, cardiovascular events, quality of life and mortality (PICO 2).

Level of evidence of the literature
Body weight, blood pressure, diabetes, clinical symptoms, osteoporosis, cardiovascular events, cortisol levels, quality of life, mortality
The level of evidence for the comparison adrenalectomy versus medication could not be assessed for the selected outcomes since no appropriate studies were found (PICO 1).
The level of evidence for the comparison adrenalectomy of the most affected side versus bilateral adrenalectomy could not be assessed for the selected outcomes since no appropriate studies were found (PICO 2).

Conclusions
Body weight, blood pressure, diabetes, clinical symptoms, osteoporosis, cardiovascular events, cortisol levels, quality of life, mortality

- **GRADE**	No evidence was found regarding the effects of adrenalectomy when compared with medication in patients with ACTH-independent Cushing's syndrome with bilateral adrenal enlargement (PICO 1). No evidence was found regarding the effects of adrenalectomy of the most affected side compared with bilateral adrenalectomy in patients with ACTH-independent Cushing's syndrome with bilateral adrenal enlargement who are eligible for surgery (PICO 2). *Source: -*

Overwegingen – van bewijs naar aanbeveling

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

Het is tot op heden onduidelijk wat de optimale behandeling voor het ACTH-onafhankelijk syndroom van Cushing op basis van bilaterale bijniervergroting is. Literatuuronderzoek leverde geen studies op die een directe vergelijking maakten tussen een adrenalectomie en medicatie (steroid synthese remmers) bij deze patiëntengroep waarin lichaamsgewicht, klinische symptomen of cardiovasculaire events werden gerapporteerd. Ook leverde literatuurstudies geen studies op die een directe vergelijking maakten tussen het verwijderen van de grootste bijnier en een bilaterale resectie wanneer de patiënt in aanmerking komt voor chirurgie.

Rekening houdend met het gebrek aan vergelijkende data, zijn beschikbare observationele 'single arm' studies gebruikt om pragmatische/praktische aanbevelingen te doen, die tevens zijn gebaseerd op "expert-opinion".

Hoewel in de meeste gevallen niet beschouwd als eerstelijnsbehandeling, kan een bilaterale adrenalectomie een essentiële behandelingsoptie zijn voor patiënten met een refractair syndroom van Cushing. Het analyseren van literatuur uit drie decennia geeft aan dat bilaterale adrenalectomie een gerechtvaardigde veilige procedure is en onmiddellijk en grotendeels betrouwbaar succes biedt (Mishra, 2007; Paduraru, 2016; Porterfield, 2008). Beschikbare gegevens over het terugkeren van functionerend bijnierweefsel, incidentie van complicaties op lange termijn en strategieën om deze complicaties te voorkomen zijn dubbelzinnig en tonen de noodzaak aan van verdere studies. Sterfte moet worden geanalyseerd in een population-based studie cohort. De sterfte is onevenredig hoog in het eerste jaar na bilaterale Cushing, vandaar dat de klinische zorg zich moet richten op patiënten in deze periode (Ritzel, 2013). The American Association of Endocrine Surgeons Guidelines for Adrenalectomy stellen voor om bij patiënten met bilaterale macronodulaire hyperplasie een unilaterale laparoscopische adrenalectomie te overwegen als een poging om biochemische remissie van hypercortisolisme te bereiken zonder permanente bijnierinsufficiëntie te veroorzaken (Yip, 2022).

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

Het voordeel van een bilaterale adrenalectomie bij patiënten met een ACTH-onafhankelijk syndroom van Cushing is dat de kans op een complete biochemische remissie het grootst is. Het komt echter wel met een prijs van een verhoogd risico op complicaties en zelfs sterfte. Het voordeel van een unilaterale adrenalectomie (van de meest aangedane bijnier) is dat er een gerede kans bestaat op biochemische genezing zonder bijnierschorsinsufficiëntie.

Bij de beslissing tot bilaterale of unilaterale adrenalectomie dient de voorkeur van de patiënt ook in ogenschouw genomen te worden ('samen beslissen'). Voor- en nadelen van beide behandelingen moeten vooraf met de patiënt besproken worden waarbij deze ook een persoonlijke afweging kan maken.

Kosten (middelenbeslag)

De kosten afweging hier betreft met name de kosten voor levenslange medicatie bij een bijnierschorsinsufficiëntie bij een bilaterale bijnierresectie.

Aanvaardbaarheid, haalbaarheid en implementatie

Overeenkomstig andere internationale wetenschappelijke organisaties achten wij het niet aanvaardbaar om patiënten een behandeling aan te bieden met een potentiële kans op sterfte (bijnierschorsinsufficiëntie bij bilaterale adrenalectomie) als er een goed alternatief is, nl een enkelzijdige adrenalectomie van de bijnier met de grootste afwijking.

Aanbeveling

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

De literatuur is niet eenduidig in een aanbeveling voor de chirurgische behandeling van patiënten met bilaterale bijniervergroting. Een bilaterale adrenalectomie lost in de regel wel het biochemische probleem op; de mate van complicaties/sterfte is echter wel significant hoog in deze groep. Een unilaterale adrenalectomie van de bijnier met de grootste laesie om een biochemische remissie van hypercortisolisme te bereiken zonder permanente bijnierschorsinsufficiëntie te veroorzaken, lijkt de beste weg om te bewandelen.

Overweeg bij patiënten met een ACTH-onafhankelijk syndroom van Cushing op basis van een bilaterale bijniervergroting, een unilaterale adrenalectomie van de bijnier met de grootste laesie om een biochemische remissie van hypercortisolisme te bereiken zonder permanente bijnierschorsinsufficiëntie te veroorzaken.

Literatuur

Mishra AK, Agarwal A, Gupta S, Agarwal G, Verma AK, Mishra SK. Outcome of adrenalectomy for Cushing's syndrome: experience from a tertiary care center. World J Surg. 2007 Jul;31(7):1425-32. doi: 10.1007/s00268-007-9067-6. Epub 2007 May 30. PMID: 17534556.

Paduraru DN, Nica A, Carsote M, Valea A. Adrenalectomy for Cushing's syndrome: do's and don'ts. J Med Life. 2016 Oct-Dec;9(4):334-341. PMID: 27928434; PMCID: PMC5141390.

Porterfield JR, Thompson GB, Young WF Jr, Chow JT, Fryrear RS, van Heerden JA, Farley DR, Atkinson JL, Meyer FB, Abboud CF, Nippoldt TB, Natt N, Erickson D, Vella A, Carpenter PC, Richards M, Carney JA, Larson D, Schleck C, Churchward M, Grant CS. Surgery for Cushing's syndrome: an historical review and recent ten-year experience. World J Surg. 2008 May;32(5):659-77. doi: 10.1007/s00268-007-9387-6. PMID: 18196319.

Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, Reincke M. Clinical review: Outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab. 2013 Oct;98(10):3939-48. doi: 10.1210/jc.2013-1470. Epub 2013 Aug 16. PMID: 23956347.

Yip L, Duh QY, Wachtel H, Jimenez C, Sturgeon C, Lee C, Velázquez-Fernández D, Berber E, Hammer GD, Bancos I, Lee JA, Marko J, Morris-Wiseman LF, Hughes MS, Livhits MJ, Han MA, Smith PW, Wilhelm S, Asa SL, Fahey TJ 3rd, McKenzie TJ, Strong VE, Perrier ND. American Association of Endocrine Surgeons Guidelines for Adrenalectomy: Executive Summary. JAMA Surg. 2022 Oct 1;157(10):870-877. doi: 10.1001/jamasurg.2022.3544. PMID: 35976622; PMCID: PMC9386598.

Bijlagen bij module Behandeling Cushing

Evidence tables
Niet van toepassing.

Table of excluded studies

Reference	Reason for exclusion
Alexandraki KI, Grossman AB. Therapeutic Strategies for the Treatment of Severe Cushing's Syndrome. Drugs. 2016 Mar;76(4):447-58. doi: 10.1007/s40265-016-0539-6. PMID: 26833215.	Wrong study design (non-systematic review)
Bancos I, Alahdab F, Crowley RK, Chortis V, Delivanis DA, Erickson D, Natt N, Terzolo M, Arlt W, Young WF Jr, Murad MH. THERAPY OF ENDOCRINE DISEASE: Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: a systematic review and meta-analysis. Eur J Endocrinol. 2016 Dec;175(6):R283-R295. doi: 10.1530/EJE-16-0465. Epub 2016 Jul 22. PMID: 27450696.	Wrong P (subclinical Cushing)
Guerin C, Taieb D, Treglia G, Brue T, Lacroix A, Sebag F, Castinetti F. Bilateral adrenalectomy in the 21st century: when to use it for hypercortisolism? Endocr Relat Cancer. 2016 Feb;23(2):R131-42. doi: 10.1530/ERC-15-0541. PMID: 26739832.	Wrong study design (non-systematic review)
Iacobone M, Citton M, Scarpa M, Viel G, Boscaro M, Nitti D. Systematic review of surgical treatment of subclinical Cushing's syndrome. Br J Surg. 2015 Mar;102(4):318-30. doi: 10.1002/bjs.9742. Epub 2015 Feb 2. PMID: 25640696.	Wrong P (subclinical Cushing)
Morelli V, Arosio M, Chiodini I. Cardiovascular mortality in patients with subclinical Cushing. Ann Endocrinol (Paris). 2018 Jun;79(3):149-152. doi: 10.1016/j.ando.2018.03.005. Epub 2018 Mar 30. PMID: 29606280.	Wrong study design (non-systematic review)
Morelli V, Frigerio S, Aresta C, Passeri E, Pugliese F, Copetti M, Barbieri AM, Fustinoni S, Polledri E, Corbetta S, Arosio M, Scillitani A, Chiodini I. Adrenalectomy Improves Blood Pressure and Metabolic Control in Patients With Possible Autonomous Cortisol Secretion: Results of a RCT. Front Endocrinol (Lausanne). 2022 Jun 2;13:898084. doi: 10.3389/fendo.2022.898084. PMID: 35721734; PMCID: PMC9202594.	Wrong P (adrenal incidentaloma)
Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A; Endocrine Society. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015 Aug;100(8):2807-31. doi: 10.1210/jc.2015-1818. Epub 2015 Jul 29. PMID: 26222757; PMCID: PMC4525003.	Wrong study design (guideline)

Paduraru DN, Nica A, Carsote M, Valea A. Adrenalectomy for Cushing's syndrome: do's and don'ts. J Med Life. 2016 Oct-Dec;9(4):334-341. PMID: 27928434; PMCID: PMC5141390.	Wrong study design (non-systematic review)
Perysinakis I, Marakaki C, Avlonitis S, Katseli A, Vassilatou E, Papanastasiou L, Piaditis G, Zografos GN. Laparoscopic adrenalectomy in patients with subclinical Cushing syndrome. Surg Endosc. 2013 Jun;27(6):2145-8. doi: 10.1007/s00464-012-2730-5. Epub 2013 Jan 26. PMID: 23355146.	Wrong P (subclinical Cushing)
Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, Reincke M. Clinical review: Outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab. 2013 Oct;98(10):3939-48. doi: 10.1210/jc.2013-1470. Epub 2013 Aug 16. PMID: 23956347.	Wrong/no comparison as in the PICO

Literature search strategy

Algemene informatie

Richtlijn: Diagnostiek en chirurgische behandeling Bijniertumoren	
Uitgangsvraag: Wat is de rol van chirurgie bij patiënten met of ACTH afhankelijke of ACTH onafhankelijke Cushing?	
Database(s): Ovid/Medline, Embase	Datum:9-1-2023
Periode: 2010-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: Cushing EN chirurgie EN volwassenen Het sleutelartikel van Reincke wordt niet gevonden omdat het een conference paper betreft. Qua terminologie wordt de paper wel gevonden. A critical reappraisal of bilateral adrenalectomy for ACTH-dependent Cushing's syndrome. Reincke M, Ritzel K, Oßwald A, Berr C, Stalla G, Hallfeldt K, Reisch N, Schopohl J, Beuschlein F.Eur J Endocrinol. 2015 Oct;173(4):M23-32. doi: 10.1530/EJE-15-0265. Epub 2015 May 20.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 9-1-2023 met relevante zoektermen gezocht vanaf 2010 naar systematische reviews en RCTs over de chirurgische behandeling van volwassen patiënten met Cushing. De literatuurzoekactie leverde 332 unieke treffers op.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	248	117	254
RCTs	74	48	78
Observationele studies			
Overig			
Totaal			332

Zoekstrategie

Embase

No.	Query	Results
#18	#16 AND #17 artikel Reincke niet gevonden	1
#17	#9 OR #10 OR #11	1792
#16	#14 OR #15 sleutelartikelen	2
#15	a AND critical AND reappraisal AND of AND bilateral AND adrenalectomy AND for AND 'acth dependent' AND cushing* AND syndrome.	1
#14	american AND association AND of AND endocrine AND surgeons AND guidelines AND for AND adrenalectomy AND executive AND summary AND 2022	1
#13	#11 NOT #10 NOT #9	1451
#12	#10 NOT #9 RCT	74
#11	#4 AND (#7 OR #8)	1619
#10	#4 AND #6	107
#9	#4 AND #5 SR	248
#8	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	13755893
#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#6	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR	733409

	literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
#4	#3 AND [1-1-2010]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT (('adolescent'/exp OR 'child'/exp OR adolescent*:ti,ab,kw OR child*:ti,ab,kw OR schoolchild*:ti,ab,kw OR infant*:ti,ab,kw OR girl*:ti,ab,kw OR boy*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenager*:ti,ab,kw OR youth*:ti,ab,kw OR pediatr*:ti,ab,kw OR paediatr*:ti,ab,kw OR puber*:ti,ab,kw) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp OR adult*:ti,ab,kw OR man:ti,ab,kw OR men:ti,ab,kw OR woman:ti,ab,kw OR women:ti,ab,kw))	4049
#3	#1 AND #2	13251
#2	'surgery'/exp OR 'surgical patient'/exp OR 'surgical risk'/exp OR 'surgery'/lnk OR 'adrenalectomy'/exp OR 'adrenal enucleation':ti,ab,kw OR 'adrenalectom*':ti,ab,kw OR 'adrenal retroperitoneoscop*':ti,ab,kw OR surgic*:ti,ab,kw OR surger*:ti,ab,kw OR operation*:ti,ab,kw OR operative:ti,ab,kw OR presurg*:ti,ab,kw OR preoperati*:ti,ab,kw OR perisurg*:ti,ab,kw OR perioperati*:ti,ab,kw OR postsurg*:ti,ab,kw OR postoperati*:ti,ab,kw OR laparoscop*:ti,ab,kw	7415112
#1	'cushing syndrome'/exp OR 'cushing disease'/exp OR cushing*:ti,ab,kw OR 'adrenal cortex hyperplasia':ti,ab,kw OR 'adrenal cortical hyperplasia':ti,ab,kw OR 'adrenocorticohyperplasia':ti,ab,kw OR 'arenocortical hyperplasia':ti,ab,kw OR 'corticotroph pituitary adenom*':ti,ab,kw OR 'pituitary acth hypersecreti*':ti,ab,kw OR 'pituitary-dependent hypercortisol*':ti,ab,kw	30198

Ovid/Medline

#	Searches	Results
14	12 not 11 RCT	48
13	(7 or 8) and 10	942
12	6 and 10	62
11	5 and 10 SR	117
10	limit 9 to yr="2010 -Current"	2396
9	3 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) not ((Adolescent/ or Child/ or Infant/ or adolescen*.ti,ab,kf. or child*.ti,ab,kf. or schoolchild*.ti,ab,kf. or infant*.ti,ab,kf. or girl*.ti,ab,kf. or boy*.ti,ab,kf. or teen.ti,ab,kf. or teens.ti,ab,kf. or teenager*.ti,ab,kf. or youth*.ti,ab,kf. or pediatr*.ti,ab,kf. or paediatr*.ti,ab,kf. or puber*.ti,ab,kf.) not (Adult/ or adult*.ti,ab,kf. or man.ti,ab,kf. or men.ti,ab,kf. or woman.ti,ab,kf. or women.ti,ab,kf.))	6007
8	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5324402
7	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4330206
6	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1574889
5	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or	639972

	literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
4	3 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	6484
3	1 and 2	6720
2	exp Specialties, Surgical/ or Adrenalectomy/ or (surgical or surger* or operation* or operative or laparoscop*).ti,ab,kf. or adrenal enucleation.ti,ab,kf. or adrenalectomy.ti,ab,kf. or adrenal retroperitoneoscop*.ti,ab,kf.	2815773
1	exp Cushing Syndrome/ or Pituitary ACTH Hypersecretion/ or hypercortisolism*.ti,ab,kf. or cushing*.ti,ab,kf. or adrenal cortex hyperplasia.ti,ab,kf. or adrenal cortical hyperplasia.ti,ab,kf. or adrenocortical hyperplasia.ti,ab,kf. or adrenocorticohyperplasia.ti,ab,kf. or arenocortical hyperplasia.ti,ab,kf. or corticotroph pituitary adenom*.ti,ab,kf. or pituitary acth hypersecreti*.ti,ab,kf. or pituitary-dependent hypercortisol*.ti,ab,kf.	21180

Module 5 – Autonome cortisol (hyper)secretie (subklinische Cushing)

Uitgangsvraag
Wanneer dient er tot resectie over gegaan te worden bij milde autonome cortisol (hyper)secretie, voorheen subklinische Cushing genoemd?

Inleiding
Autonome cortisol hypersecretie is een endocriene stoornis welke kan worden gevonden bij patiënten met een bijnierincidentaloom. Deze incidentalomen kunnen leiden tot ACTH-onafhankelijk verhoogde cortisol secretie, welke geen klassieke klachten geven maar wel metabole problemen kunnen geven met daarbij een verhoogd risico op cardiovasculaire events en osteoporose. In deze module wordt er een handvat gegeven in het management van het incidentaloom met autonome cortisol (hyper)secretie.

Search and select
A systematic review of the literature was performed to answer the following question: What are the beneficial and harmful effects of surgery compared to watchful waiting in patients with subclinical Cushing's Syndrome on cardiovascular events, diabetes and osteoporosis?

P (Patients)	Patients with autonomous cortisol (hyper)secretion (subclinical Cushing) and detected adrenal lesion
I (Intervention)	Adrenalectomy
C (Control)	No adrenalectomy, follow-up
O (Outcomes)	Hypertension, blood pressure, diabetes, dyslipidemia, cardiovascular diseases (intermediate outcomes), osteoporosis, myocardial infarction, cerebrovascular accident, mortality

<u>Relevant outcome measures</u>
The guideline development group considered hypertension, blood pressure, diabetes, and dyslipidemia as critical outcome measures for decision making; and osteoporosis, myocardial infarction, cerebrovascular accident, and mortality as important outcome measures for decision making.

The working group defined the outcome measures as follows:
- hypertension: number of patients with hypertension
- blood pressure: systolic and diastolic blood pressure
- diabetes: number of patients with diabetes
- dyslipidemia: number of patients with dyslipidemia
- osteoporosis: number of patients with osteoporosis
- myocardial infarction: incidence
- cerebrovascular accident: incidence
- mortality: death rate

The guideline development group defined the following differences as a minimal clinically (patient) important difference:
- hypertension: GRADE standard limits of 25% for dichotomous outcome measures (RR <0.80 or RR >1.25)
- blood pressure: 10 mmHg
- diabetes: GRADE standard limits of 25% for dichotomous outcome measures (RR <0.80 or RR >1.25)

- dyslipidemia: GRADE standard limits of 25% for dichotomous outcome measures (RR <0.80 or RR >1.25)
- osteoporosis: GRADE standard limits of 25% for dichotomous outcome measures (RR <0.80 or RR >1.25)
- myocardial infarction: Absolute difference >5% for lethal complications, or >25% for serious complications.
- cerebrovascular accident: Absolute difference >5% for lethal complications, or >25% for serious complications.
- mortality: Absolute difference >5%

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 04-10-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 153 hits. Studies were selected based on the following criteria: systematic reviews or RCT's comparing adrenalectomy versus no adrenalectomy or follow-up in patients with autonomous cortisol (hyper)secretion (subclinical Cushing) and detected adrenal lesion. In total, eighteen studies were initially selected based on title and abstract screening. After reading the full text, fifteen studies were excluded (see the table with reasons for exclusion under the tab Methods), and three studies were included.

Results
Three 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
Systematic reviews
The systematic review by **Bancos (2016)** studied the effect of adrenalectomy on cardiovascular risk factors compared with conservative management in patients with adrenal tumors and subclinical Cushing's syndrome. Original prospective and retrospective, comparative and non-comparative studies, containing at least five patients who underwent adrenalectomy, which analyzed adults with either non-functioning adrenal tumors or adrenal tumors with subclinical Cushing, and reporting outcomes of interest before and after adrenalectomy, were eligible for inclusion. Nonoriginal studies and case reports were excluded from the systematic review and meta-analysis. Electronic searches were performed in MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trial, Cochrane Database of Systematic Reviews, and Scopus on 17 November 2015. Outcome measures of interest were: hypertension, pre-diabetes or diabetes mellitus, obesity, dyslipidemia, systolic blood pressure, diastolic blood pressure, body mass index, weight, fasting glucose concentrations, glycosylated hemoglobin, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Data of 16 retrospective cohort studies, 9 prospective cohort studies and 1 randomized controlled trial, including a total of 584 patients with subclinical Cushing's syndrome were included in the systematic review of Bancos (2016).
Of these 26 studies, 10 studies meet our PICO criteria (Azaka, 2011; Chiodini, 2010; Giordano, 2010; Guerrieri, 2010; Iacobone, 2012; Kawate, 2014; Ricciato, 2014; Rossi, 2000; Toniato, 2009; Tsuiki, 2008). Six were retrospective cohort studies, three were prospective cohort studies and one was a randomized controlled trial. These studies were performed in Italy (n=7) and Japan (n=3). Meta-analyses were performed for multiple outcome measures. Subgroup analyses were performed in three subgroups of patients stratified based on dexamethasone

suppression test cortisol cutoff, for the outcome measures hypertension and diabetes mellitus type 2. Important limitations of the current review were that definitions of subclinical Cushing's syndrome were heterogenous, there were significant differences between studies in how and when the outcomes of interest were assessed, definitions of comorbidities and of improvement were inconsistent, it was unclear what exactly conservative management was, and individual variables such as age, gender, and tumor size were not consistently reported.

The systematic review by **Khan (2019)** investigated the prevalence of cardiometabolic outcomes in nonfunctioning and subclinical cortisol secreting adrenal incidentalomas (AIs), comparing adrenalectomy to conservative treatment. Original retrospective, prospective, or cross-sectional studies, which analyzed patients with nonfunctioning and/or subclinical cortisol secreting adrenal incidentalomas, that reported at least two components of metabolic syndrome (diabetes, impaired glucose tolerance, fasting hyperinsulinemia, dyslipidemia, hypertension, and obesity/central adiposity) and the results of adrenalectomy or conservative management on these outcomes, were eligible for inclusion. Studies without biochemically confirmed subclinical hypercortisolism, studies only reporting preoperative data or insufficient postoperative data, and case series and case reports including fewer than 10 operated patients were excluded. Electronic searches were performed in MEDLINE, Cochrane Controlled Trials Register (1960-2005), and EMBASE (1991-2005) from the date of each database's inception up to June 2018. Outcome measures were: prevalence of components of metabolic syndrome in subclinical cortisol secreting AIs and nonfunctioning AIs, and cardiometabolic outcomes of conservative management and adrenalectomy (diabetes, impaired glucose tolerance, fasting hyperinsulinemia, dyslipidemia, hypertension, and obesity/central adiposity). Data of 15 cohort studies, 1 randomized controlled trial, and 2 cross-sectional studies, including a total of 1722 patients were included. Of these 18 studies, 5 studies meet our PICO criteria, of which 4 studies are already included through Bancos (2016). Therefore, only 1 study was left to include (**Petramala, 2017**). This retrospective cohort study was performed in Italy. Khan (2019) did not perform any meta-analyses or subgroup analyses because of heterogeneity between the studies. Important limitations of the current review were the heterogeneity in definitions of subclinical cortisol secreting and in definitions of endpoints and outcomes, variation in follow-up length, variation in medical treatment for cardiovascular risk factors, and the content of conservative management.

RCTs

Morelli (2022) performed a randomized clinical trial to study the metabolic effect of adrenalectomy in patients with adrenal incidentalomas with possible autonomous cortisol secretion. Patients with age between 40 and 75 years, and diagnosis by imaging of unilateral AI larger than 1 cm with radiological features at computed tomography consistent with an adrenocortical adenoma (homogeneous and hypodense, Hounsfield units <10 or with proven radiological dimensional stability) were eligible for trial participation. In total, 62 patients were eligible and were randomized into two groups. The intervention group (n=31) received adrenalectomy intervention, in which the AI was removed. The control group (n=31) received the conservative approach, in which patients with borderline-elevated blood pressure or grade 1 hypertension, prediabetes, or overweight were suggested to follow intensive lifestyle behavior changes, and patients with grade 2-3 hypertension, not fully controlled diabetes, obesity, or dyslipidemia were addressed to cardiologists and/or diabetologists. The duration of the follow-up was 6 months. The study reported the following relevant outcome measures: patients with obesity, body weight change, patients with dyslipidemia, dyslipidemia control, systolic blood pressure, diastolic blood pressure, patients with hypertension, hypertension grade, blood pressure control, patients with diabetes mellitus, patients with impaired glucose tolerance/impaired fasting glucose, diabetes mellitus grade, glycometabolic control, and the

association between blood pressure control improvement and surgical or conservative approach (adjusted for possible confounders).

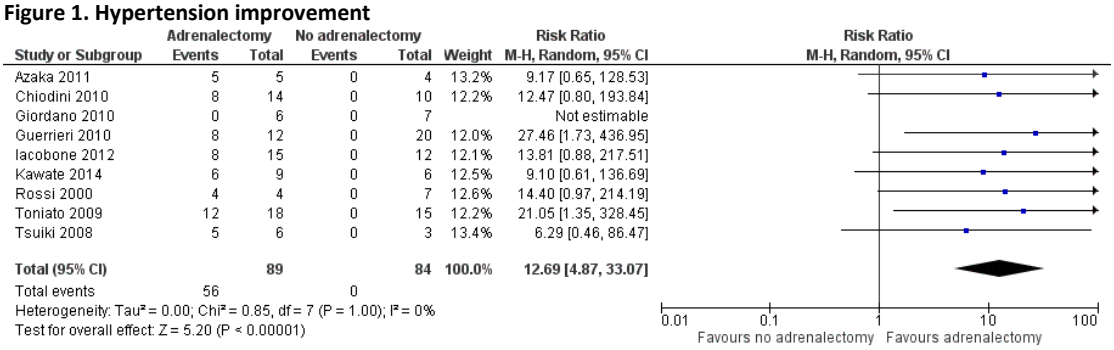
Results

Hypertension (critical)

Three studies reported the outcome measure hypertension (Bancos, 2016; Morelli, 2022; Petramala, 2017). Due to heterogenous presentation of the results, the results were not pooled, but presented separately.

Bancos (2016) reported hypertension improvement in nine studies. In total, 55 of 89 patients with hypertension who underwent adrenalectomy had hypertension improvement, and 0 of 84 patients with hypertension who did not undergo adrenalectomy had hypertension improvement. Pooled data of these nine studies showed a pooled risk ratio of 12.69 (95% CI 4.87 to 33.07), in favour of the patients who underwent adrenalectomy (Figure 1). This difference is considered clinically relevant.

Figure 1. Hypertension improvement



Z: p-value of overall effect; df: degrees of freedom; I2: statistical heterogeneity; CI: confidence interval.

Petramala (2017) reported patients with hypertension. At baseline, 22 of the 26 patients (85%) who underwent adrenalectomy had hypertension, and 28 of the 44 patients (63.1%) who did not undergo adrenalectomy had hypertension. At follow-up, 15 of the 26 patients (58.82%) who underwent adrenalectomy had hypertension, and 32 of the 44 patients (72.5%) who did not undergo adrenalectomy had hypertension. The risk ratio at follow-up was 0.79 (95% CI 0.54 to 1.15), in favour of the patients who underwent adrenalectomy. This difference is considered clinically relevant.

Morelli (2022) reported the amount of patients with hypertension. In total, 14 of the 25 patients (56%) who underwent adrenalectomy had hypertension, and 22 of the 30 patients (73%) who did not undergo adrenalectomy had hypertension. The risk ratio was 0.76 (95% CI 0.51 to 1.15), in favour of the patients who underwent adrenalectomy. This difference is considered clinically relevant.

Blood pressure (critical)

Two studies reported several blood pressure outcome measures (Bancos, 2016; Morelli, 2022). These outcomes are presented separately, and results were not pooled due to heterogenous presentation of the outcomes.

Systolic blood pressure

Two studies reported the outcome measure systolic blood pressure (Bancos, 2016; Morelli, 2022). As only two studies were included, the results were not pooled.

Bancos (2016) reported systolic blood pressure. The mean difference between the group of patients who underwent adrenalectomy and the group of patients who did not undergo adrenalectomy was -12.546 mmHg (95% CI -18.589 to -6.502), in favour of the patients who underwent adrenalectomy. This difference is considered clinically relevant.

Morelli (2022) reported systolic blood pressure. The patients who underwent adrenalectomy (n=25) had a mean systolic blood pressure of 133.2 mmHg (SD ± 12.8 mmHg). The patients who did not undergo adrenalectomy (n=30) had a mean systolic blood pressure of 142.9 mmHg (SD ± 16.7 mmHg). The mean difference between the groups was -9.70 mmHg (95% CI -17.50 to -1.90), in favour of the patients who underwent adrenalectomy. This difference is not considered clinically relevant.

Diastolic blood pressure

Two studies reported the outcome measure diastolic blood pressure (Bancos, 2016; Morelli, 2022). As only two studies were included, the results were not pooled.

Bancos (2016) reported diastolic blood pressure. The mean difference between the group of patients who underwent adrenalectomy and the group of patients who did not undergo adrenalectomy was -9.298 mmHg (95% CI -15.123 to -3.472), in favour of the patients who underwent adrenalectomy. This difference is not considered clinically relevant.

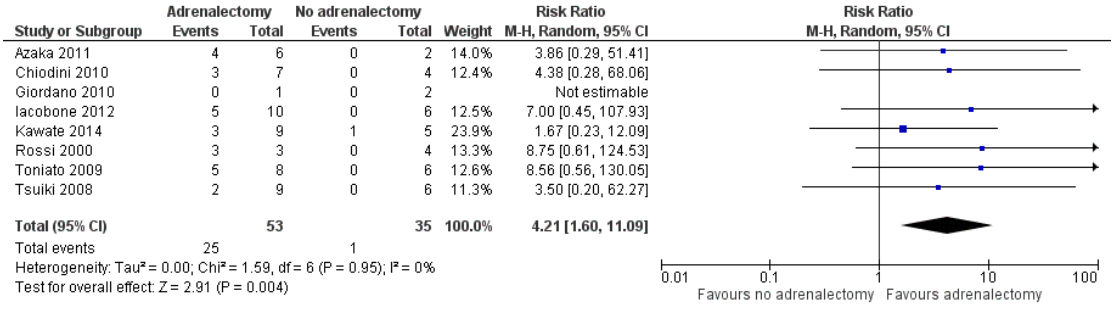
Morelli (2022) reported diastolic blood pressure. The patients who underwent adrenalectomy (n=25) had a mean diastolic blood pressure of 77.1 mmHg (SD ± 8.9 mmHg). The patients who did not undergo adrenalectomy (n=30) had a mean diastolic blood pressure of 78 mmHg (SD ± 10.7 mmHg). The mean difference between the groups was -0.90 mmHg (95% CI -6.08 to 4.28), in favour of the patients who underwent adrenalectomy. This difference is not considered clinically relevant.

Diabetes Mellitus (critical)

Three studies reported the outcome measure Diabetes Mellitus (Bancos, 2016; Morelli, 2022; Petramala, 2017). Due to study heterogeneity, the results were not pooled.

Bancos (2016) reported Diabetes Mellitus improvement in eight studies. In total, 25 of 53 patients with diabetes who underwent adrenalectomy had Diabetes Mellitus improvement, and 1 of 35 patients with diabetes who did not undergo adrenalectomy had Diabetes Improvement. Pooled data of these eight studies showed a pooled risk ratio of 4.21 (95% CI 1.60 to 11.09), in favour of the patients who underwent adrenalectomy (Figure 2). This difference is considered clinically relevant.

Figure 2. Diabetes Mellitus improvement



Z: p-value of overall effect; df: degrees of freedom; I2: statistical heterogeneity; CI: confidence interval.

Petramala (2017) reported Diabetes Mellitus improvement, normalization, or worsening. At baseline, 10 of the 26 patients (38%) who underwent adrenalectomy had diabetes, and 11 of the 44 patients (25%) who did not undergo adrenalectomy had diabetes. The risk ratio at baseline was 1.54 (95% CI 0.76 to 3.12), in favour of the patients who did not undergo adrenalectomy. At follow-up, 6 of the 26 patients (23.5%) who underwent adrenalectomy had diabetes, and 17 of the 44 patients (38.5%) who did not undergo adrenalectomy had diabetes. The risk ratio at follow-up was 0.60 (95% CI 0.27 to 1.32), in favour of the patients who underwent adrenalectomy. This difference is considered clinically relevant.

Morelli (2022) reported the amount of patients with Diabetes Mellitus. In total, 5 of the 25 patients (20%) who underwent adrenalectomy had Diabetes Mellitus, and 6 of the 30 patients (20%) who did not undergo adrenalectomy had Diabetes Mellitus. The risk ratio was 1.00 (95% CI 0.35 to 2.89). This means there was no difference between the groups.

Dyslipidemia (critical)
Two studies reported the outcome measure dyslipidemia (Bancos, 2016; Morelli, 2022).

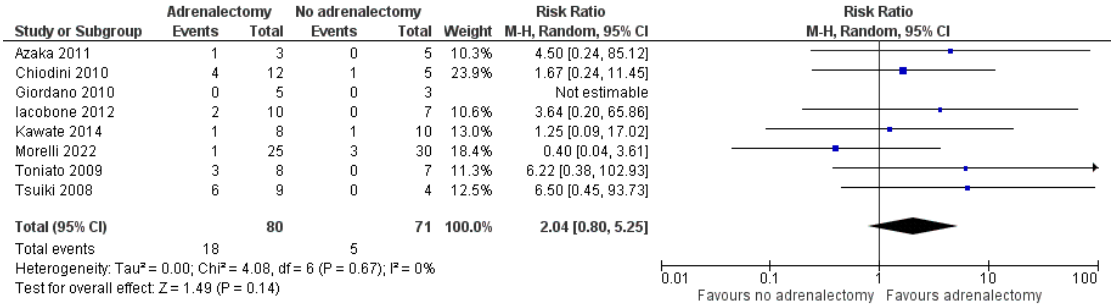
Bancos (2016) reported dyslipidemia improvement in seven studies. In total, 18 of 80 patients with dyslipidemia who underwent adrenalectomy had dyslipidemia improvement, and 5 of 71 patients with dyslipidemia who did not undergo adrenalectomy had dyslipidemia improvement.

Morelli (2022) reported the amount of patients with dyslipidemia. In total, 15 of the 25 patients (60%) who underwent adrenalectomy had dyslipidemia, and 20 of the 30 patients (66.7%) who did not undergo adrenalectomy had dyslipidemia. The risk ratio was 0.90 (95% CI 0.60 to 1.35), in favour of the patients who underwent adrenalectomy. This difference is not considered clinically relevant.

Morelli (2022) reported dyslipidemia control. In total, 23 of the 25 patients (92%) who underwent adrenalectomy had a stable dyslipidemia level, and 23 of the 30 patients (76.7%) who did not undergo adrenalectomy had a stable dyslipidemia level. In total, 1 of the 25 patients (4%) who underwent adrenalectomy had a worse dyslipidemia level, and 4 of the 30 patients (13.3%) who did not undergo adrenalectomy had a worse dyslipidemia level. In total, 1 of the 25 patients (4%) who underwent adrenalectomy had an improved dyslipidemia level, and 3 of the 30 patients (10%) who did not undergo adrenalectomy had an improved dyslipidemia level (Figure 3). The risk ratio was 0.40 (95% CI 0.04 to 3.61), in favour of the patients who underwent adrenalectomy. This difference is considered clinically relevant. The p-value for dyslipidemia control was 0.31.

Pooled data of these eight studies showed a pooled risk ratio of 2.04 (95% CI 0.80 to 5.25), in favour of the patients who underwent adrenalectomy (Figure 3). This difference is considered clinically relevant.

Figure 3. Dyslipidemia improvement



Z: p-value of overall effect; df: degrees of freedom; I2: statistical heterogeneity; CI: confidence interval.

Osteoporosis (important)
None of the studies reported the outcome measure osteoporosis.

Myocardial infarction (important)
None of the studies reported the outcome measure myocardial infarction.

Cerebrovascular accident (important)
None of the studies reported the outcome measure cerebrovascular accident.

Mortality (important)
None of the studies reported the outcome measure mortality.

Level of evidence of the literature
The level of evidence regarding the outcome measure was based on systematic revies of observational studies and an RCT and therefore starts low.

Hypertension (critical)
The level of evidence was downgraded by 2 levels because of study limitations (risk of bias, -1), and because the confidence interval exceeds the level for clinical relevance (imprecision, -1). The level of evidence is therefore very low.

Blood pressure (critical)
Systolic blood pressure and diastolic blood pressure
The level of evidence was downgraded by 2 levels because of study limitations (risk of bias, -1), and because the confidence interval exceeds the levels for clinical relevance (imprecision, -1). The level of evidence is therefore very low.

Diabetes Mellitus (critical)
The level of evidence was downgraded by 2 levels because of study limitations (risk of bias, -1), and because of the small amount of included patients (imprecision, -1). The level of evidence is therefore very low.

Dyslipidemia (critical)
The level of evidence was downgraded by 3 levels because of study limitations (risk of bias, -1), and because the confidence interval exceeds the levels for clinical relevance (imprecision, -2). The level of evidence is therefore very low.

Osteoporosis (important)
The level of evidence regarding the outcome measure osteoporosis could not be graded, as the included studies did not report this outcome measure.

Myocardial infarction (important)
The level of evidence regarding the outcome measure myocardial infarction could not be graded, as the included studies did not report this outcome measure.

Cerebrovascular accident (important)
The level of evidence regarding the outcome measure cerebrovascular accident could not be graded, as the included studies did not report this outcome measure.

Mortality (important)
The level of evidence regarding the outcome measure mortality could not be graded, as the included studies did not report this outcome measure.

Conclusions
Hypertension (critical)

Very low GRADE	The evidence is very uncertain about the effect of adrenalectomy on hypertension when compared with no adrenalectomy in patients with autonomous cortisol (hyper)secretion (subclinical Cushing) and detected adrenal lesion. *Source: Bancos, 2016; Morelli, 2022; Petramala, 2017*

Blood pressure (critical)
Systolic blood pressure and diastolic blood pressure

Very low GRADE	The evidence is very uncertain about the effect of adrenalectomy on systolic blood pressure when compared with no adrenalectomy in patients with autonomous cortisol (hyper)secretion (subclinical Cushing) and detected adrenal lesion. *Source: Bancos, 2016; Morelli, 2022*

Diabetes Mellitus (critical)

Very low GRADE	The evidence is very uncertain about the effect of adrenalectomy on Diabetes Mellitus when compared with no adrenalectomy in patients with autonomous cortisol (hyper)secretion (subclinical Cushing) and detected adrenal lesion. *Source: Bancos, 2016; Morelli, 2022; Petramala, 2017*

Dyslipidemia (critical)

Very low GRADE	The evidence is very uncertain about the effect of adrenalectomy on dyslipidemia when compared with no adrenalectomy in patients with autonomous cortisol (hyper)secretion (subclinical Cushing) and detected adrenal lesion. *Source: Bancos, 2016; Morelli, 2022*

Osteoporosis (important)

No GRADE	No evidence was found regarding the effect of adrenalectomy on osteoporosis when compared with no adrenalectomy in patients with

	autonomous cortisol (hyper)secretion (subclinical Cushing) and detected adrenal lesion. *Source: -*

Myocardial infarction (important)

No GRADE	No evidence was found regarding the effect of adrenalectomy on myocardial infarction when compared with no adrenalectomy in patients with autonomous cortisol (hyper)secretion (subclinical Cushing) and detected adrenal lesion. *Source: -*

Cerebrovascular accident (important)

No GRADE	No evidence was found regarding the effect of adrenalectomy on cerebrovascular accident when compared with no adrenalectomy in patients with autonomous cortisol (hyper)secretion (subclinical Cushing) and detected adrenal lesion. *Source: -*

Mortality (important)

No GRADE	No evidence was found regarding the effect of adrenalectomy on mortality when compared with no adrenalectomy in patients with autonomous cortisol (hyper)secretion (subclinical Cushing) and detected adrenal lesion. *Source: -*

Overwegingen – van bewijs naar aanbeveling

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

Er is een literatuuronderzoek verricht naar de vergelijking tussen adrenalectomie versus geen adrenalectomie bij patiënten met autonome cortisol (hyper)secretie (subklinische Cushing) en gedetecteerde bijnier laesie. Er zijn twee systematische reviews op basis van observationeel onderzoek en één RCT geïncludeerd die deze vergelijking hebben onderzocht. Voor de cruciale uitkomstmaten werd gevonden dat patiënten die een adrenalectomie hadden ondergaan vaker verbetering van bloeddruk, diabetes en dyslipidemie hadden (niet altijd klinisch relevant). Voor de belangrijke uitkomstmaten osteoporose, myocardinfarct, beroerte en mortaliteit werd geen bewijs gevonden. Voor alle uitkomstmaten was de bewijskracht zeer laag, hier ligt dus een kennislacune. De lage bewijskracht werd met name veroorzaakt door beperkingen in de studies en resultaten van lage precisie. Door de zeer lage bewijskracht zal de keuze voor het wel of niet behandelen met adrenalectomie dus afhangen van andere factoren, zoals bijvoorbeeld comorbiditeiten van de patiënt of de eigen voorkeur van de patient. Bij patiënten bij wie er een hoog (anesthesiologisch) operatierisico is, zal de voorkeur niet uitgaan naar een operatie. Denk hierbij aan comorbiditeiten zoals cardiopulmonale aandoeningen of morbide obesitas. Voor patiënten bij wie het gevonden incidentaloom op basis van verricht onderzoek (beeldvorming, labonderzoek) een verhoogde kans heeft dat het een maligniteit betreft, of middels biochemische activiteit leidt tot klinische klachten, gelden de aanbevelingen gedaan in de overige modulen van deze richtlijn.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Het besluit tot al dan niet een adrenalectomie moet in goed overleg met de patiënt genomen worden. De voorkeuren van de patiënt zijn hierin van groot belang. Wat de beste voortgang is na de bevinding van een (goedaardig) bijnierincidentaloom met autonome, subklinische cortisol productie, is niet met bewijs onderbouwd en met zekerheid te zeggen. Het is wel mede afhankelijk van de mate van cortisol overproductie en de duur en aanwezigheid van comorbiditeiten zoals hypertensie, diabetes, lipidemie, eventueel osteoporose, etc. Met name moeilijk behandelbare diabetes en moeilijk behandelbare hypertensie zou een aanvullende reden tot operatie kunnen zijn.

Kosten (middelenbeslag)
Kosteneffectiviteit van een dergelijke adrenalectomie dient afgezet te worden tegen de behaalde QALY's door de postoperatief mogelijk beter controleerbare diabetes, tensie- en lipidenwaarden. Hierin zal meegenomen moeten worden de kosten die eventueel bespaard worden bij minder medicatiegebruik. De genoemde klachten betreffen een zeer breed spectrum en de ervaren klachten door patiënten lopen vermoedelijk zeer uiteen, daarom is het niet goed mogelijk een homogene studiepopulatie te vinden waarbij dergelijke kosten tussen de interventies adequaat vergeleken kunnen worden. De werkgroep is van mening dat een hogere toename van comorbiditeit op basis van de autonome cortisol overproductie wel sneller de aan de operatie gerelateerde kosten zou kunnen rechtvaardigen. Daarin dient echter te worden meegenomen dat naast de financiele kosten, ook rekening gehouden moet worden met het (eenmalig) verhoogde complicatierisico.

Aanvaardbaarheid, haalbaarheid en implementatie
Verschillende studies tonen aan dat er een verbetering optreedt van de cruciale uitkomstmaten dyslipidemie, hypertensie en diabetes na een verrichte adrenalectomie bij patiënten met subklinische Cushing. De kosten van een operatie wegen zeker op tegen de macro-economische lasten van bovengenoemde uitkomstmaten. Een eventuele toename van chirurgische ingrepen op basis van deze diagnose kan in potentie een langere wachttijd impliceren; we verwachten echter niet dat dit tot grote problemen zal leiden.

Aanbeveling
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Meerdere studies tonen een verbetering van de cruciale uitkomstmaten dyslipidemie, hypertensie en diabetes na verrichte adrenalectomie bij patiënten met subklinische Cushing. Getuige de relatieve lage betrouwbaarheid van deze uitkomstmaten kan de werkgroep echter niet zonder meer een adrenalectomie aanbevelen als best beschikbare therapie. Keuze hierover blijft een gezamenlijke overweging van arts en patient, welke in goed overleg genomen dient te worden en vermoedelijk mede afhankelijk zal zijn van de door patiënt ervaren klachten in het kader van zijn/haar comorbiditeiten. Ten aanzien van osteoporose, myocardinfarct of herseninfarct is geen bewijs aan te dragen voor een verminderd risico of ziektelast na het uitvoeren van een adrenalectomie. De werkgroep kan derhalve geen chirurgie adviseren ter preventie van deze uitkomstmaten.

Overweeg een adrenalectomie, te bespreken in een multidisciplinair overleg bij voorkeur in hierop gespecialiseerd centrum, bij een patiënt met autonome cortisol productie op basis van een bijnierincidentaloom, mede in het kader van eventuele andere (cardiovasculaire) risicofactoren (bloeddruk en lipidenspectrum), osteoporose en diabetes. Factoren die bij de individuele patiënt meegenomen moeten worden met betrekking tot de behandelbeslissing zijn:

- Leeftijd

- Geslacht
- Gezondheid
- Comorbiditeiten (hypertensie, osteoporose, diabetes)
- Uitslag dexamethason suppressie test (cortisol >50 nmol/l)
- Voorkeur van de patiënt

Pas adequate secundaire preventie en follow-up toe bij patiënten met autonome cortisol productie van een bijnierincidentaloom op cardiovasculaire risicofactoren, osteoporose en diabetes.

Literatuur

Bancos I, Alahdab F, Crowley RK, Chortis V, Delivanis DA, Erickson D, Natt N, Terzolo M, Arlt W, Young WF Jr, Murad MH. THERAPY OF ENDOCRINE DISEASE: Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: a systematic review and meta-analysis. Eur J Endocrinol. 2016 Dec;175(6):R283-R295. doi: 10.1530/EJE-16-0465. Epub 2016 Jul 22. PMID: 27450696.

Khan U. Nonfunctioning and Subclinical Cortisol Secreting Adrenal Incidentalomas and their Association with Metabolic Syndrome: A Systematic Review. Indian J Endocrinol Metab. 2019 May-Jun;23(3):332-346. doi: 10.4103/ijem.IJEM_52_19. PMID: 31641636; PMCID: PMC6683688.

Morelli V, Frigerio S, Aresta C, Passeri E, Pugliese F, Copetti M, Barbieri AM, Fustinoni S, Polledri E, Corbetta S, Arosio M, Scillitani A, Chiodini I. Adrenalectomy Improves Blood Pressure and Metabolic Control in Patients With Possible Autonomous Cortisol Secretion: Results of a RCT. Front Endocrinol (Lausanne). 2022 Jun 2;13:898084. doi: 10.3389/fendo.2022.898084. PMID: 35721734; PMCID: PMC9202594.

Bijlagen bij module Autonome cortisol (hyper)secretie (subklinische Cushing)

Evidence tables

Systematic reviews

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Khan, 2019	SR of 15 cohort studies, 1 RCT, and 2 cross-sectional studies *Literature search up to June 2018* **A**: Toniato, 2009 **B**: Iacobone, 2012 **C**: Kawate, 2014 **D**: Petramala, 2017 **E**: Tsuiki, 2008 <u>Study design:</u> Systematic review <u>Setting and country:</u> **A**: Italy **B**: Italy **C**: Japan **D**: Italy **E**: Japan <u>Source of funding:</u> Nil.	<u>Inclusion criteria SR:</u> Original retrospective, prospective, or cross-sectional studies, analyzing patients with nonfunctioning and/or subclinical cortisol secreting Adrenal Incidentalomas (AIs), reporting at least two components of metabolic syndrome (diabetes, impaired glucose tolerance, fasting hyperinsulinemia, dyslipidemia, HTN, and obesity/central adiposity), and the results of adrenalectomy and/or conservative	Intervention: Surgery: adrenalectomy.	Control: Conservative management.	<u>Duration of follow-up:</u> **A**: Mean 7.7 years (range 2-17 years) **B**: Intervention mean 54 ± 34 months, control 56 ± 37 months **C**: Median 5.3 years **D**: Mean 12 months (range 9-15 months) **E**: Intervention 7-19 months (average 13 ± 3.8 months), control 15-69 months (average 27 ± 15.2 months) <u>For how many participants were no complete outcome data available?</u> Not reported.	<u>Hypertension:</u> Defined as: **A**: Systolic blood pressure >150 and diastolic blood pressure >90 **B, C**: Systolic blood pressure ≥140, diastolic blood pressure ≥90 or antihypertensive treatment. **E**: Systolic blood pressure >140 and/or diastolic blood pressure >90 **A**: Intervention: Improved 7 (38.9%), normalized 5 (27.8%) Control: worsened 5 (22.7%) P=0.046 **B**: Control: worsened 3/12 (25%) P=0.002 **C**: Intervention: improved 6 (67%) Control: improved 0 (0%), worsened 4 (67%) **D**: Baseline: Intervention: 85% Control: 63.1% Follow-up: Intervention: 58.82%	The author concludes that cardiometabolic risk factors should be screened for in patients with subclinical cortisol secreting AIs. In general, adrenalectomy data indicated improvement in metabolic complications in patients with subclinical cortisol secreting AI. Metabolic complications deteriorated or did not improve in patients who were treated conservatively. No GRADE performed. No meta-analysis and sensitivity analysis performed. Age, gender, and size of the AI might influence cardiovascular outcomes, but subgroup analysis was not possible, as the individual studies did not consistently report these variables.

	Conflicts of interest: None declared.	management on these outcomes included. Exclusion criteria SR: Studies without biochemically confirmed subclinical hypercortisolism, studies reporting only preoperative data or insufficient postoperative data, case reports and case series including fewer than 10 operated patients. *5 studies included* Important patient characteristics at baseline: Study size (n): **A**: Intervention 23, control 22 **B**: Intervention 15, control 20 **C**: Intervention 15, control 12 **D**: Intervention 26, control 44 **E**: Intervention 10, control 12 Age (years):				Control: 72.5% P<0.05 **E**: Intervention: improved 5 Control: worsened 1, developed HTN 1 Diabetes mellitus: Defined as: **A**: Fasting glucose >126 mg/dl or treatment with antidiabetic drugs **B**: FPG >126 mg/dl or treatment with antidiabetic drugs **C**: FPG ≥126 mg/dl and/or random glucose ≥200 mg/dl and/or HbA1c ≥6.5% and/or treatment with antidiabetic drugs **E**: FPG >126 mg/dl or 2h plasma glucose >200 mg/dl **A**: Intervention: improved 3 (37.5%), normalized 2 (25%) Control: worsened 2 (9%) P=0.619 **B**: Control: worsened 3/12 (25%) P=0.032 **C**: Intervention: improved 3 (60%) Control: improved 1 (20%), worsened 2 (40%) **D**: Baseline: Intervention: 38% Control: 25% Follow-up: Intervention 23.5% Control: 38.5%	

		A: Intervention 63 ± 4.1, control 64 ± 1.8 **B**: Intervention median 57 (range 36-78), control median 58 (range 39-75) **C**: Intervention 55.3 ± 9.4, control 66.3 ± 8.8 **D**: 61.9 ± 8.4 **E**: Median 59.7 (range 43-74) Sex of participants (male): **A**: Intervention 12, control 10 **B**: Intervention 12, control 8 **C**: Intervention 2, control 6 **D**: 52 **E**: 6				<u>Hypercholesterolemia (data retrieved from Toniato, 2009)</u> **A**: Intervention: normalized 3 (37.5%) Control: worsened 3 (13.6%) P=0.619 <u>Dyslipidemia</u> Defined as: **A**: Triglycerides >150 mg/dl, HDL <40 mg/dl in men, HDL <50 mg/dl in women **B**: Triglycerides ≥150 mg/dl, HDL <40 mg/dl in men, HDL <50 mg/dl in women, patients on anti-dyslipidemic treatment **C**: Total cholesterol ≥220 mg/dl and/or LDL ≥140 mg/dl and/or HDL <40 mg/dl and/or triglycerides ≥150 mg/dl, treatment with lipid-lowering medication **E**: Total cholesterol >220 mg/dl **B**: Baseline: Intervention: 10 (50%) Control: 7 (46.7%) Follow-up: Control: no change P=0.47 **C**: Baseline: Intervention: 8 (53%) Control: 10 (83%) Follow-up: Intervention: 1 improvement (13%) Control: 1 improvement (10%)2, 2 worsening (20%) **E**: Baseline: Intervention: 9 (90%)	

						Control: 6 (50%) Follow-up: Intervention: 6 improvement Control: none worsened, 2 developed P<0.001 <u>Obesity</u> Defined as: **A**: Overweight: BMI 25-30 kg/m^2, obese: BMI >30 kg/m^2 **B**: Overweight: BMI 25-29.9 kg/m^2, obese: ≥30 kg/m^2 **C**: Obesity: BMI ≥25 kg/m^2 **E**: Obesity: BMI ≥25 kg/m^2 **A**: Intervention: BMI normalized 3 (50%) **B**: Control: BMI worsened 3/12 (25%) P=0.19 **C**: Baseline: Intervention: 5 (33%) Control 5 (42%) **D**: Baseline: Intervention: 53.8% Control: 33% Follow-up: Intervention: 24.5% Control: 42.7% P<0.05 **E**: Baseline: Intervention: 3 (30%) Control: 3 (25%) Follow-up: Intervention: 0 improvement Control: none worsened, 2 developed <u>Metabolic syndrome</u> Defined as:	

						D: Defined by ATP III-NCEP criteria **D**: Baseline: Intervention 54% Control 39% Follow-up: Intervention: 23% Control: 45% P<0.05 <u>High triglycerides</u> **D**: Baseline: Intervention: 34% Control: 34% Follow-up: Intervention: 27% Control: 38% <u>Impaired glucose metabolism (data retrieved from Tsuiki, 2008):</u> **E**: Baseline: Intervention: 9 (90%) Control: 6 (50%) Follow-up: Intervention: 2 Control: 1 worsened, 2 developed	
Bancos, 2016 [individual study characteristics deduced from Bancos, 2016]	SR and meta-analysis of 6 cohort studies *Literature search up to 17 November 2015* **A**: Rossi, 2000 **B**: Guerrieri, 2010 **C**: Giordano, 2010 **D**: Chiodini, 2010 **E**: Azaka, 2011 **F**: Ricciato, 2014	<u>Inclusion criteria SR:</u> Original prospective and retrospective, comparative and non-comparative studies, adults with either non-functioning adrenal tumors or adrenal tumors with subclinical cushing, at least	Intervention: Adrenalectomy	Control: Conservative management	<u>End-point of follow-up</u>: Most studies reassessed patients 6 months after surgery, with a mean follow-up of 28 (1-109) months (median or mean follow-up was reported in only 11 studies). <u>For how many participants were no complete outcome data available?</u> Not reported.	<u>Hypertension improvement</u> Defined as: **A**: Decrease in the dose, number of discontinuation of medications. **B**: Before and after SBP and DBP means/SD, P values, and magnitude of change reported. **C**: Not defined. **D**: Change of HTN grade (European Society Cardology Mean SBP and DBP before and after.	<u>Facultative</u>: The authors conclude that a beneficial effect of adrenalectomy compared to conservative management on cardiovascular risk factors in patients with subclinical Cushing's syndrome is suggested. No GRADE performed. Subgroup analyses were performed for

	Study design: 2 prospective cohort studies and 4 retrospective cohort studies Setting and Country: **A**: Italy **B**: Italy **C**: Italy **D**: Italy **E**: Japan **F**: Italy Source of funding: No specific grant from any funding agency in the public, commercial or not-for-profit sector was received. Conflicts of interest: Authors have no conflicts of interest to declare. IB, WA and MT are members of the European Society of Endocrinology and European Network for the Study of Adrenal Tumors Clinical Guideline Panel.	five patients undergoing adrenalectomy, outcomes of interest before and after adrenalectomy reported. Exclusion criteria SR: Nonoriginal studies and case reports. *6 studies included* Important patient characteristics at baseline: N patients **A**: Intervention: n=5, control: n=7 **B**: Intervention: n=19, control: n=28 **C**: Intervention: n=6, control: n=10 **D**: Intervention: n=25, control: n=16 **E**: Intervention: n=8, control: n=8 **F**: Intervention: n=16, control: n=17 Definition of subclinical Cushing's syndrome:				**E**: Decrease in blood pressure <140/90 mmHg leading to decrease of the dose, number or discontinuation of medications. **F**: Before and after blood pressure measurements, reduction or discontinuation of blood pressure meds. **A**: Intervention: 4/4 Control: 0/7 RR 14.400 [95% CI 0.968 to 214.193] **B**: Intervention: 8/12 Control: 0/20 RR 27.462 [95% CI 1.726 to 436.947] **C**: Intervention: 0/6 Control: 0/7 RR 1.143 [95% CI 0.026 to 50.397] **D**: Intervention: 8/14 Control: 0/10 RR 12.467 [95% CI 0.802 to 193.845] **E**: Intervention: 5/5 Control: 0/4 RR 9.167 [95% CI 0.654 to 128.533] Diabetes Mellitus improvement Defined as: **A**: Reduction of oral medications or insulin. **B**: P values and magnitude of change reported to fasting plasma glucose. **C**: Not defined.	dexamethasone suppression test (DST) cortisol cutoff. The three groups were: 1. Cortisol cutoff ≥3 µg/dL, 83 nmol/L 2. Cortisol cutoff <3 µg/dL, 83 nmol/L 3. Studies that did not report DST cortisol cutoff or did not provide how SCS was defined. Subgroup analysis was performed for outcomes hypertension (HTN) and diabetes mellitus type 2 (DM2). Patients in the three subgroups experienced similar rates of HTN and DM2 improvement following adrenalectomy. Heterogeneity was low for the outcome measures reported.

		A: Overnight dexamethasone: 3 µg/dL (2 mg), UFC >2 SD above normal range, ACTH Low, Average daily cortisol. **B**: Not defined. **C**: Overnight dexamethasone: 1.8 µg/dL (1 mg), UFC >100 µg/24h, ACTH <5 pg/mL, Loss of circadian cortisol rhythm. **D**: Overnight dexamethasone: 3 µg/dL (1 mg), UFC >70 µg/24h, ACTH <10 pg/mL. **E**: Overnight dexamethasone: 3 µg/dL (1 mg), cortisol cutoff 1 µg/dL, Normal basal cortisol AND one of: low DHEA-S, low ACTH, loss of circadian cortisol rhythm, unilateral uptake on scintigraphy. **F**: Overnight dexamethasone: 1.8 µg/dL (1 mg), UFC >137 µg/24h, ACTH <10 pg/mL, Midnight serum cortisol >50 µg/mL.				**D**: Fasting plasma glucose considered changed if move from one category to another according to Adult Treatment Panel III criteria Fasting plasma glucose mean before and after. **E**: Normoglycemia (glucose <110 mg/dL) on OGTT, HbA1c decreased by >0.3% or discontinuation/decrease of medications. **F**: Change in glucose level. **A**: Intervention: 3/3 Control: 0/4 RR 8.750 [95% CI 0.615 to 124.534] **C**: Intervention: 0/1 Control: 0/2 RR 1.500 [95% CI 0.046 to 49.070] **D**: Intervention: 3/7 Control: 0/4 RR 4.375 [95% CI 0.281 to 68.058] **E**: Intervention: 4/6 Control: 0/2 RR 3.875 [95% CI 0.289 to 51.407] <u>Dyslipidemia improvement</u> Defined as: **A**: Not reported. **B**: P values and magnitude of change reported for HDL. **C**: Not defined. **D**: Move from one category to another based on Adult Treatment Panel III criteria LDL means before and after.	

		Groups comparable at baseline: not reported.				**E**: LDL <140 mg/dL, trigs <150 mg/dL; HDL>40 or discontinuation/decrease of medications. **F**: Before and after mean HDL and TG. **C**: Intervention: 0/5 Control: 0/3 RR 0.667 [95% CI 0.016 to 27.240] **D**: Intervention: 4/12 Control: 1/5 RR 1.667 [95% CI 0.243 to 11.448] **E**: Intervention: 1/3 Control: 0/5 RR 4.500 [95% CI 0.238 to 85.117] <u>Obesity improvement</u> Defined as: **A**: Not reported. **B**: Before and after mean BMI/SDs, P values, and magnitude of change reported. **C**: Not defined. **D**: Improvement = greater than 5% decrease in body weight, body weight before and after mean. **E**: Weight decrease by ≥3 kg **F**: Before and after mean BMIs. **D**: Intervention: 4/12 Control: 1/8 RR 2.667 [95% CI 0.361 to 19.712] **E**: Intervention: 2/2 Control: 0/1	

						RR 3.333 [95% CI 0.287 to 38.752] <u>Systolic blood pressure:</u> **B**: MD -10.000 [95% CI -17.250 to -2.750] **D**: MD -22.800 [95% CI -37.780 to -7.820] **F**: MD -14.300 [95% CI -36.054 to 7.454] <u>Diastolic blood pressure:</u> **D**: MD -14.900 [95% CI -25.082 to -4.718] **F**: MD -4.800 [95% CI -15.431 to 5.831] <u>Fasting blood glucose:</u> **D**: MD -31.600 [95% CI -56.031 to -7.169] **F**: MD -12.100 [95% CI -37.944 to 13.744]	

RCT

Study reference	**Study characteristics**	**Patient characteristics [2]**	**Intervention (I)**	**Comparison / control (C) [3]**	**Follow-up**	**Outcome measures and effect size [4]**	**Comments**
Morelli, 2022	Data from a randomized clinical trial <u>Setting and country:</u> Fondazione IRCCS Ca' Granda, Milan, Italy, IRCCS Istituto	<u>Inclusion criteria</u>: Age between 40 and 75 years, and diagnosis by imaging of unilateral Adrenal Incidentaloma (AI) larger than 1 cm with radiological features at computed tomography consistent with an adrenocortical	Intervention: adrenalectomy	Control: Conservative approach. Patients with borderline-elevated BP or grade 1 hypertension, with prediabetes, or with overweight were suggested to follow intensive lifestyle behaviour changes. Patients with grade 2-3 hypertension, with not fully controlled diabetes, with obesity, or with dyslipidemia were	<u>Length of follow-up</u>: 6 months. <u>Loss-to-follow-up</u>: Intervention: N=6 (19.4%) Reasons: consent withdrawal (n=4),	<u>Patients with obesity:</u> Intervention: 6 (24.0) Control: 7 (23.3) P=1.00 <u>Body weight change (stable/worse/better):</u> Intervention: 19/2/4 (76/8/16)	

	Ortopedico Galeazzi, Milan, Italy, and IRCCS "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Foggia, Italy. Source of funding Funded by the Grant RF 2013-02356606 from the Italian Ministry of Health to IC, VM, AS, and SC. Conflicts of interest: IC received consulting fees from Corcept Therapeutics and HRA Pharma. The remaining authors declare they have no conflicts of interest.	adenoma (homogeneous and hypodense, Hounsfield units <10 or with proven radiological dimensional stability). Exclusion criteria: Hypogonadism, thyrotoxicosis, chronic renal failure and hepatic disease, alcoholism, rheumatologic and hematological disease, and eating disorders, including binge eating disorder, bulimia nervosa, and anorexia nervosa, intake of drugs influencing cortisol and dexamethasone metabolism or cortisol secretion, signs or symptoms specific to hypercortisolism, possible metastatic diseases or radiologic appearance not consistent with an adrenocortical adenoma, biochemical evidence of pheochromocytoma and aldosteronoma, ACTH dependency, and incomplete diagnostic work-up, and patients with AI larger than 5 cm. N total at baseline: Intervention: 31 Control: 31		addressed to cardiologists and/or diabetologists. Patients received personalised treatment.	cancer occurrence (n=1), death for COVID-19 (n=1) Control: N=1 (3.2%) Reasons: adrenalectomy for adenoma enlargement (n=1) Incomplete outcome data: No incomplete outcome data.	Control: 26/1/3 (86.7/3.3/10) P=0.48 Patients with dyslipidemia: Intervention: 15 (60) Control: 20 (66.7) P=0.41 DL control (stable/worse/better): Intervention: 23/1/1 (92/4/4) Control: 23/4/3 (76.7/13.3/10) P=0.31 SBP (mmHg): Intervention: 133.2 ± 12.8 (105-160) Control: 142.9 ± 16.7 (110-170) P=0.02 DBP (mmHg): Intervention: 77.1 ± 8.9 (60-90) Control: 78 ± 10.7 (60-100) P=0.74 Patients with HT: Intervention: 14 (56) Control: 22 (73) P=0.14 HT grade: Intervention: 0.6 ± 0.5 (0-2) Control: 1.1 ± 0.8 (0-2) P=0.02	

		<u>Important prognostic factors[2]</u>: Age ± SD: Intervention: 62.5 ± 10.4 Control: 66.1 ± 9.1 Sex (female): Intervention: 68 Control: 80 Patients with obesity (%): Intervention: 8 (26.7) Control: 8 (32) Patients with DL (%): Intervention: 15 (60) Control: 21 (70) SBP (mmHg): Intervention: 139.1 ± 14.0 (100-170) Control: 139.7 ± 15.3 (110-165) DBP (mmHg): Intervention: 82.2 ± 10.1 (70-100) Control: 77.7 ± 10.2 (60-97) Patients with HT (%): Intervention: 16 (64) Control: 22 (73) Patients with diabetes (%): Intervention: 5 (20) Control: 6 (20)				<u>BP control (stable/worse/better):</u> Intervention: 7/1/17 (28/4/68) Control: 18/8/4 (60/26.7/13.4) P=0.001 <u>Patients with DM:</u> Intervention: 5 (20) Control: 6 (20) P=1.00 <u>Patients with IGT/IFG:</u> Intervention: 5 (20) Control: 10 (33.3) P=0.37 <u>DM grade:</u> Intervention: 0.8 ± 1.2 (0-3) Control: 1.1 ± 1.2 (0-4) P=0.34 <u>GL control (stable/worse/better):</u> Intervention: 16/2/7 (64/8/28) Control: 23/6/1 (76.7/20/3.3) P=0.03 <u>Association blood pressure control improvement with surgical or conservative approach:</u> - Surgical approach (yes): OR 3.0 [95% CI 3.8 to 108.3] P<0.001 - Hypertension (yes/no):	

		Patients with IGT/IFG (%): Intervention: 7 (28) Control: 9 (30) Groups were comparable at baseline.				OR 1.2 [95% CI 0.20 to 6.21] P=0.90 - Diabetes (yes/no): OR 2.34 [95% CI 0.33 to 16.52] P=0.40	

Risk of bias tables

Systematic reviews

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Khan, 2019	Yes Reason: Inclusion criteria and research question are predefined. PICO and research question only match for part of the studies in the SR.	Yes Reason: Search period and strategy are described, multiple databases, including Medline, were searched.	No Reason: Excluded studies are not referenced.	Yes Reason: Study characteristics of included studies are described.	No Reason: No multivariate analysis performed.	Yes Reason: NIH quality assessment tool for observational cohort and cross-sectional studies was used.	No Reason: Clinical heterogeneity exists between studies. Studies are not pooled.	No Reason: Publication bias was not assessed.	No Reason: Sources of support (nil) were reported for the SR but not for every individual study.
Bancos, 2016	Yes Reason: Inclusion criteria and research question are predefined. PICO and research question only match for part of the studies in the SR.	Yes Reason: Search period and strategy are described, multiple databases, including Medline, were searched.	No Reason: Excluded studies are not referenced.	Yes Reason: Study characteristics of included studies are described.	No Reason: No multivariate analysis performed.	Yes Reason: Newcastle-Ottawa tool was used to assess the quality of included observational studies.	Yes Reason: Low statistical heterogeneity for pooled data.	No Reason: Publication bias was not assessed.	No Reason: Sources of support were reported for the SR but not for every individual study.

RCT

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Morelli, 2022	Definitely yes Reason: Block randomization was used.	No information Reason: Not reported.	No information Reason: Not reported.	Definitely no Reason: Loss-to-follow-up in intervention group was 19.4% and in control group was 3.2%.	Probably yes Reason: All outcomes in the methods section are reported in the results.	Probably no Reason: Treatments in control group were not standardized, study bias might exist.	**HIGH** Due to lack of information about allocation concealment and blinding, high loss-to-follow-up, and other bias that might exist.

Table of excluded studies

Reference	Reason for exclusion
Thompson LH, Ranstam J, Almquist M, Nordenström E, Bergenfelz A. Impact of Adrenalectomy on Morbidity in Patients with Non-Functioning Adrenal Cortical Tumours, Mild Hypercortisolism and Cushing's Syndrome as Assessed by National and Quality Registries. World J Surg. 2021 Oct;45(10):3099-3107. doi: 10.1007/s00268-021-06214-0. Epub 2021 Jun 27. PMID: 34180008; PMCID: PMC8408086.	Does not match with PICO: no comparison with no surgery or follow-up
Sheikh-Ahmad M, Dickstein G, Matter I, Shechner C, Bejar J, Reut M, Sroka G, Laniado M, Saiegh L. Unilateral Adrenalectomy for Primary Bilateral Macronodular Adrenal Hyperplasia: Analysis of 71 Cases. Exp Clin Endocrinol Diabetes. 2020 Dec;128(12):827-834. doi: 10.1055/a-0998-7884. Epub 2019 Oct 21. PMID: 31634962.	Does not match with PICO: SR on unilateral adrenalectomy for primary bilateral macronodular adrenal hyperplasia
Morelli V, Arosio M, Chiodini I. Cardiovascular mortality in patients with subclinical Cushing. Ann Endocrinol (Paris). 2018 Jun;79(3):149-152. doi: 10.1016/j.ando.2018.03.005. Epub 2018 Mar 30. PMID: 29606280.	Wrong publication type: communication
Loh HH, Yee A, Loh HS, Sukor N, Kamaruddin NA. The natural progression and outcomes of adrenal incidentaloma: a systematic review and meta-analysis. Minerva Endocrinol. 2017 Mar;42(1):77-87. doi: 10.23736/S0391-1977.16.02394-4. Epub 2015 Dec 23. PMID: 26698544.	Does not match with PICO: no comparison with surgery
Thomas AZ, Blute ML Sr, Seitz C, Habra MA, Karam JA. Management of the Incidental Adrenal Mass. Eur Urol Focus. 2016 Feb;1(3):223-230. doi: 10.1016/j.euf.2015.12.006. Epub 2016 Feb 3. PMID: 28723391.	Wrong publication type: communication
Guerin C, Taieb D, Treglia G, Brue T, Lacroix A, Sebag F, Castinetti F. Bilateral adrenalectomy in the 21st century: when to use it for hypercortisolism? Endocr Relat Cancer. 2016 Feb;23(2):R131-42. doi: 10.1530/ERC-15-0541. PMID: 26739832.	Does not match with PICO: no comparison of surgery with follow-up
Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016 Aug;175(2):G1-G34. doi: 10.1530/EJE-16-0467. PMID: 27390021.	Wrong publication type: guideline
Iacobone M, Citton M, Scarpa M, Viel G, Boscaro M, Nitti D. Systematic review of surgical treatment of subclinical Cushing's syndrome. Br J Surg. 2015	Does not add studies to Bancos (2016)

Mar;102(4):318-30. doi: 10.1002/bjs.9742. Epub 2015 Feb 2. PMID: 25640696.	
Shen J, Sun M, Zhou B, Yan J. Nonconformity in the clinical practice guidelines for subclinical Cushing's syndrome: which guidelines are trustworthy? Eur J Endocrinol. 2014 Oct;171(4):421-31. doi: 10.1530/EJE-14-0345. Epub 2014 Jul 1. PMID: 24986532.	Wrong publication type: overview of guidelines
Di Dalmazi G, Berr CM, Fassnacht M, Beuschlein F, Reincke M. Adrenal function after adrenalectomy for subclinical hypercortisolism and Cushing's syndrome: a systematic review of the literature. J Clin Endocrinol Metab. 2014 Aug;99(8):2637-45. doi: 10.1210/jc.2014-1401. Epub 2014 May 30. PMID: 24878052.	Does not match with PICO: no comparison of surgery with follow-up
Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, Reincke M. Clinical review: Outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab. 2013 Oct;98(10):3939-48. doi: 10.1210/jc.2013-1470. Epub 2013 Aug 16. PMID: 23956347.	Does not match with PICO: SR on outcomes of bilateral adrenalectomy in Cushing's Syndrome
Perysinakis I, Marakaki C, Avlonitis S, Katseli A, Vassilatou E, Papanastasiou L, Piaditis G, Zografos GN. Laparoscopic adrenalectomy in patients with subclinical Cushing syndrome. Surg Endosc. 2013 Jun;27(6):2145-8. doi: 10.1007/s00464-012-2730-5. Epub 2013 Jan 26. PMID: 23355146.	Does not match with PICO: no comparison with no surgery or follow-up
Chiodini I. Clinical review: Diagnosis and treatment of subclinical hypercortisolism. J Clin Endocrinol Metab. 2011 May;96(5):1223-36. doi: 10.1210/jc.2010-2722. Epub 2011 Mar 2. PMID: 21367932.	Wrong publication type: narrative review
Toniato A, Merante-Boschin I, Opocher G, Pelizzo MR, Schiavi F, Ballotta E. Surgical versus conservative management for subclinical Cushing syndrome in adrenal incidentalomas: a prospective randomized study. Ann Surg. 2009 Mar;249(3):388-91. doi: 10.1097/SLA.0b013e31819a47d2. PMID: 19247023.	Included in the review of Khan (2019)
Tabarin A, Bardet S, Bertherat J, Dupas B, Chabre O, Hamoir E, Laurent F, Tenenbaum F, Cazalda M, Lefebvre H, Valli N, Rohmer V; French Society of Endocrinology Consensus. Exploration and management of adrenal incidentalomas. French Society of Endocrinology Consensus. Ann Endocrinol (Paris). 2008 Dec;69(6):487-500. doi: 10.1016/j.ando.2008.09.003. Epub 2008 Nov 20. PMID: 19022420.	Wrong publication type: consensus document, review

Literature search strategy

Zoekverantwoording

Algemene informatie

Richtlijn: NVvH Richtlijn bijniertumoren	
Uitgangsvraag: UV9 Wanneer dient er tot resectie over gegaan te worden bij subklinische Cushing?	
Database(s): Ovid/Medline, Embase	Datum:4-10-2022
Periode: 2000	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: (Bijniertumoren OF adrenalectomy) EN Cushing syndroom EN chirurgie EN volwassenen Van de 8 sleutelartikelen worden er 6 gevonden. De artikelen van Hsieh en Terzolo worden niet gevonden omdat het overzichtsartikelen betreft. In eerste instantie zijn alleen de SRs en RCts aangeboden in Rayyan.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 4-10-2022 met relevante zoektermen gezocht vanaf 2000 naar sytematische reviews en RCTs over chirurgische behandeling bij bijniertumoren en subklinisch Cushing syndroom bij volwassenen. De literatuurzoekactie leverde 153 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	110	54	108
RCTs	43	46	45
Observationele studies			
Overig			
Totaal			153

Zoekstrategie

Embase

No.	Query	Results
#56	#53 NOT #55 Artikelen Hsieh en Terzolo niet gevonden	2
#55	#53 AND #54 sleutelartikelen gevonden	6
#54	#40 OR #41 OR #42	989
#53	#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 sleutelartikelen	8
#52	beneficial AND metabolic AND effects AND of AND prompt AND surgical AND treatment AND in AND patients AND with AND chiodini	1
#51	adrenalectomy AND may AND improve AND cardiovascular AND metabolic AND impairment AND ameliorate AND quality AND of AND life AND in AND patients AND with AND adrenal AND incidentalomas AND subclinical	1
#50	cardiovascular AND risks AND their AND 'long term' AND clinical AND outcome AND in AND patients AND with AND subclinical AND syndrome AND tsuiki	1
#49	surgical AND versus AND conservative AND management AND for AND subclinical AND cushing AND syndrome AND in AND adrenal AND incidentalomas AND toniato AND 2009	1

#48	improvement AND of AND cardiovascular AND risk AND factors AND after AND adrenalectomy AND in AND patients AND with AND adrenal AND tumors AND subclinical AND syndrome AND a AND systematic AND review AND 'meta analysis'	1
#47	clinical AND benefits AND of AND unilateral AND adrenalectomy AND in AND patients AND with AND subclinical AND hypercortisolism AND due AND to AND adrenal AND incidentaloma	1
#46	2019 AND when AND to AND intervene AND for AND subclinical AND syndrome AND hsieh	1
#45	subclinical AND syndrome AND definition AND management AND terzolo AND 2011 NOT 'up to date':ti	1
#44	#42 NOT #41 NOT #40 OBS	833
#43	#41 NOT #40 RCT	43
#42	#35 AND (#38 OR #39)	703
#41	#35 AND #37	58
#40	#35 AND #36 SR	110
#39	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	13495097
#38	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#37	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814
#36	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#35	#34 AND [1-1-2000]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1809
#34	#33 NOT (('adolescent'/exp OR 'child'/exp OR adolescent*:ti,ab,kw OR child*:ti,ab,kw OR schoolchild*:ti,ab,kw OR infant*:ti,ab,kw OR girl*:ti,ab,kw OR boy*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenager*:ti,ab,kw OR youth*:ti,ab,kw OR pediatr*:ti,ab,kw OR paediatr*:ti,ab,kw OR puber*:ti,ab,kw) NOT ('adult'/exp OR 'aged'/exp OR 'middle aged'/exp OR adult*:ti,ab,kw OR man:ti,ab,kw OR men:ti,ab,kw OR woman:ti,ab,kw OR women:ti,ab,kw))	3857
#33	#31 AND #32	5686
#32	'surgery'/exp OR 'surgical patient'/exp OR 'surgical risk'/exp OR 'surgery'/lnk OR surgic*:ti,ab,kw OR surger*:ti,ab,kw OR operation*:ti,ab,kw OR operative:ti,ab,kw OR presurg*:ti,ab,kw OR preoperati*:ti,ab,kw OR 'pre-surg*':ti,ab,kw OR 'pre-operati*':ti,ab,kw OR perisurg*:ti,ab,kw OR	7305569

	perioperati*:ti,ab,kw OR 'peri-surg*':ti,ab,kw OR 'peri-operati*':ti,ab,kw OR postsurg*:ti,ab,kw OR postoperati*:ti,ab,kw OR 'post-surg*':ti,ab,kw OR 'post-operati*':ti,ab,kw OR laparoscop*:ti,ab,kw	
#31	#29 AND #30	6592
#30	'cushing syndrome'/exp OR 'hypercortisolism'/exp OR hypercortisolism*:ti,ab,kw OR 'cushing syndrome':ti,ab,kw OR 'cushing`s syndrome':ti,ab,kw OR 'cushings syndrome':ti,ab,kw OR 'adrenal cortex hyperplasia':ti,ab,kw OR 'adrenal cortical hyperplasia':ti,ab,kw OR 'adrenocortical hyperplasia':ti,ab,kw OR 'adrenocorticohyperplasia':ti,ab,kw OR 'arenocortical hyperplasia':ti,ab,kw	24712
#29	'adrenalectomy'/exp OR 'adrenal enucleation':ti,ab,kw OR 'adrenalectomy':ti,ab,kw OR 'adrenal retroperitoneoscop*':ti,ab,kw OR 'adrenal tumor'/exp OR (((adren* OR suprarenal) NEAR/4 (cancer* OR neoplasm* OR carcinoma* OR lesion* OR tumor* OR disease* OR mass* OR incidental* OR adenom* OR nodule*)):ti,ab,kw)	71841

Ovid/Medline

#	Searches	Results
13	12 not 11 not 10 OBS	1003
12	5 and (8 or 9)	1052
11	5 and 7 RCT	46
10	5 and 6 SR	54
9	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5262925
8	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4263413
7	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1552079
6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	622316
5	4 not ((Adolescent/ or Child/ or Infant/ or adolescen*.ti,ab,kf. or child*.ti,ab,kf. or schoolchild*.ti,ab,kf. or infant*.ti,ab,kf. or girl*.ti,ab,kf. or boy*.ti,ab,kf. or teen.ti,ab,kf. or teens.ti,ab,kf. or teenager*.ti,ab,kf. or youth*.ti,ab,kf. or pediatr*.ti,ab,kf. or paediatr*.ti,ab,kf. or puber*.ti,ab,kf.) not (Adult/ or adult*.ti,ab,kf. or man.ti,ab,kf. or men.ti,ab,kf. or woman.ti,ab,kf. or women.ti,ab,kf.))	3556
4	1 and 2 and 3	3887
3	exp Specialties, Surgical/ or su.fs. or (surgical or surger* or operation* or operative or laparoscop*).ti,ab,kf. or adrenal enucleation.ti,ab,kf. or adrenalectomy.ti,ab,kf. or adrenal retroperitoneoscop*.ti,ab,kf.	3794066
2	exp Cushing Syndrome/ or hypercortisolism*.ti,ab,kf. or cushing syndrome.ti,ab,kf. or cushing`s syndrome.ti,ab,kf. or cushings syndrome.ti,ab,kf. or adrenal cortex hyperplasia.ti,ab,kf. or adrenal cortical hyperplasia.ti,ab,kf. or adrenocortical hyperplasia.ti,ab,kf. or adrenocorticohyperplasia.ti,ab,kf. or arenocortical hyperplasia.ti,ab,kf.	17445

1	Adrenalectomy/ or exp Surgical Procedures, Operative/ or exp Adrenal Gland Neoplasms/ or ((adren* or suprarenal) adj4 (cancer* or neoplasm* or carcinoma* or lesion* or tumor* or disease* or mass* or incidental* or adenom* or nodule*)).ti,ab,kf.	3500848

Module 6 – Behandeling feochromocytoom

Uitgangsvraag
Wat is de waarde van preoperatieve blokkade bij patiënten met feochromocytoom?

Inleiding
Een patiënt met een feochromocytoom wordt in de meeste (internationale) centra, voordat deze geopereerd wordt, meestal klinisch voorbereid met preoperatieve blokkade. De patiënt wordt dan in een aantal weken ingesteld op medicatie, voornamelijk alfablokkers, zodat de catecholaminen die tijdens de operatie vrijkomen niet te grote tensieschommelingen teweeg kunnen brengen, met alle mogelijke gevolgen van dien (bloedingen, cardiaal falen, etc.). Kortweg is de rationale voor preoperatieve bloeddrukverlagende medicatie:

1. Symptoomverlichting
2. Bloeddrukcontrole
3. Verbeteren intraoperatieve hemodynamische stabiliteit/voorkomen perioperatieve cardiovasculaire complicaties

Toenemend lijkt er een beweging te ontstaan van groepen specialisten die een selectief deel van de patiënten niet meer “blokt” voordat zij de operatie ondergaan. De gegeven redenen hiervoor zijn onder andere de toegenomen kwaliteit van de anesthesiologie, de langdurige blokkaden en de vaak langere postoperatieve bewaking als gevolg van de medicatie geinduceerde hypotensie die door sommige onderzoekers verondersteld wordt. Wij zouden graag onderzoeken of deze strategie veilig is voor alle, danwel een subgroep van patiënten.

Search and select
A systematic review of the literature was performed to answer the following question:
What are the (un)favorable effects of pretreatment for blood pressure versus no pretreatment in patients undergoing surgery for pheochromocytoma on mortality, cardiovascular complications, length of stay and hemodynamic parameters?

P (Patients)	patients undergoing surgery for their pheochromocytoma
I (Intervention)	pretreatment for blood pressure (preoperative alpha-blockers, beta-blockers or other antihypertensives)
C (Control)	no pretreatment for blood pressure
O (Outcomes)	mortality, cardiovascular complications, length of stay, duration of hemodynamic support, hemodynamic stability

<u>Relevant outcome measures</u>
The guideline development group considered mortality and cardiovascular complications as *critical* outcome measures for decision making; and length of stay, duration of hemodynamic support and hemodynamic stability as *important* outcome measures for decision making.

The guideline development group defined the outcome measures as follows:

- Mortality: death (within 30 days) after surgery
- Cardiovascular complications: number of events (within 30 days) after surgery
  - cardiac failure
  - arrythmias
  - coronary ischaemia (angina pectoris, myocardial infarction)
  - cerebrovascular accident (ischemic/hemorrhagic)
- Length of stay: length of hospital stay in number of days

- Duration of hemodynamic support: length of stay on Medium Care Unit, Intensive Care Unit or Post Anesthesia Care Unit in number of days
- Hemodynamic stability: intraoperative hypertension, postoperative hypotension
  - systolic peaks >160 mmHg (number of episodes, duration >160 mmHg, Time Weighted Average)
  - mean arterial pressure <60 mmHg (number of episodes, duration <60 mmHg), Time Weighted Average)

The guideline development group defined the following differences as a minimal clinically (patient) important difference:

- Mortality: absolute difference of 5%
- Cardiovascular complications: absolute difference of 5%
- Length of stay: difference of 1 day of stay
- Duration of hemodynamic support: difference of 1 day of hemodynamic support
- Hemodynamic stability: difference of 15 mmHg

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until 14-03-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 355 hits. Studies were selected based on the following criteria:

- Systematic reviews, randomized controlled trials, or observational comparative studies;
- full-text English or Dutch language publication;
- complying with the PICO criteria.

Twenty-eight 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 three studies were included.

Results

One systematic review and two additional retrospective cohort 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

Schimmack (2020) conducted a systematic review and meta-analysis to determine the potential benefit of preoperative alpha-blockade compared with no treatment before adrenalectomy for phaeochromocytoma. Multiple databases (MEDLINE (via PubMed), Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL)) were searched up to December 2018. Studies comparing preoperative alpha-blockade with no blockade in adults undergoing phaeochromocytoma surgery were included. Studies evaluating mixed medical treatments were eligible if the treatment included alpha-blockade. Four retrospective non-randomized studies **(Brunaud, 2014; Groeben, 2017; Shao, 2011; Ulchaker, 1999)** with a total of 603 patients were included. As 27 patients had bilateral tumor resection, 630 procedures were performed. Two studies also included paragangliomas (extra-adrenal phaeochromocytomas) (Ulchaker, 1999; Groeben, 2017). Both selective and non-selective alpha-blockers were used. In two studies, the preoperative antihypertensive treatment also included beta-blockers (Ulchaker, 1999) and/or calcium channel blockers (Brunaud, 2014;

Ulchaker, 1999). Important patient characteristics (age, sex and tumor size) of the study populations were not comparable at baseline (see evidence table). The baseline characteristics of the groups (pretreatment vs. no pretreatment) in the separate studies were also not comparable. Other important characteristics at baseline, such as blood pressure and (nor)metanephrine concentrations were inadequately and inconsistently reported. Confounding was not addressed in the four studies. The assessed outcomes were intraoperative hypertensive crisis, mean maximal intraoperative heart rate, cardiovascular complications, and mortality. The methodological quality of included studies and the quality of the evidence for every outcome were evaluated.

Buscemi (2021) performed a retrospective observational study. Patients who underwent laparoscopic adrenalectomy for phaeochromocytoma from 2000 to 2017 were included. Planned open and bilateral adrenalectomies were excluded. Forty-nine patients were treated with preoperative alpha-blockade (selectively or non-selectively) and 14 without preoperative alpha-blockade. Age and sex ratio were comparable between the two groups, but tumour size was significantly higher in the group without alpha-blockade (see evidence table). The primary outcome was the major complication rate. Secondary outcomes were need for advanced intra-operative hemostasis, admission to the ICU, length of stay, systolic blood pressure and diastolic blood pressure. Confounding was not addressed in this study.

Groeben (2020) performed a multicenter, retrospective observational study with 1860 patients. They had surgery for phaeochromocytoma or paraganglioma between 2000 and 2017. 1517 patients underwent surgery with alpha-blockade (selectively or non-selectively) and 343 without alpha-blockade. Data on type of surgical approach and adrenal cortex-sparing resection was recorded. Separate data on groups of patients with or without alpha-blockade was only presented for the centre with the largest group of patients without alpha-blockade. In this centre, the groups were comparable at baseline regarding age, sex ratio and tumour size. The main outcomes were intraoperative hypertensive crises, and perioperative morbidity and mortality. Intra- and postoperative deaths within three months were reported. Confounding was not addressed in this study.

Results

Mortality *(critical)*
Four studies reported the outcome mortality.
One study reported the 30-day mortality rate (**Brunaud, 2014**). However, no mortality was observed in both groups. Three studies reported the perioperative mortality rate. No surgical mortalities were observed in the study of **Ulchaker (1999)** and **Buscemi (2021)**. In the study of **Groeben (2020)**, perioperative mortality was 0.5% (8 of 1517, 95% CI: 0.1 to 0.9, mostly cardiovascular causes) in pretreated patients and 0.3% (1 of 343, 95% CI: -0.3 to 0.9, pneumosepsis) in non-pretreated patients. The risk difference is 0.2%, which is not clinically relevant.

Cardiovascular complications *(critical)*
Four studies assessed cardiovascular complications.
Ulchaker (1999) reported 6 cardiovascular complications in the pretreated group (6/79, 7.6%) and no cardiovascular complications in the non-pretreated group (0/34, 0%). These complications included pulmonary edema in 3 patients, congestive heart failure in 2 patients and a cerebral vascular accident in 1 patient. The risk difference is 7.6%, which is clinically relevant.

Groeben (2020) reported a cardiovascular complication rate of 5.9% (90 of 1517, 95% CI: 4.7 to 7.1) in the pretreated group and 0.9% (3 of 343, 95% CI: -0.1 to 1.9) in the non-pretreated group. The risk difference is 5%, which is clinically relevant.
Groeben (2017) and **Buscemi (2021)** reported that no cardiovascular complications were detected in both groups.

Length of stay *(important)*
One study reported the length of stay (**Buscemi (2021)**). The median length of stay for the pretreated group was 5 days (IQR 4-6) and 4 days (IQR 4-4) for the non-pretreated group.
Hospital duration of stay was mentioned to be assessed in the study of Brunaud (2014), but was not described in the results.

Duration of hemodynamic support *(important)*
None of the studies reported duration of hemodynamic support.

Hemodynamic stability *(important)*
One study reported hemodynamic stability as defined by the guideline development group. **Brunaud (2014)** specified intraoperative hemodynamic instability (IHD) as at least one systolic blood pressure measurement >160 mm Hg and at least one episode of mean arterial pressure <60 mmHg. Episodes of IHD were observed in 54 patients (35%) in total, but the numbers were not reported per group.
Schimmack (2020) defined the outcome intraoperative hypertensive crisis as the mean maximal intraoperative SBP and mean maximal intraoperative DBP. Moreover, the mean maximal intraoperative heart rate was assessed.
Four studies in the systematic review reported on maximal intraoperative SBP. The pooled mean difference -3.75 mmHg (95% CI: -10.14 to 2.65) in favour of pretreatment (figure 1). This difference is not clinically relevant.
Three studies in the systematic review reported on maximal intraoperative DBP. The pooled mean difference was 3.33 mmHg (95% CI: -3.99 to 10.66) in favour of no pretreatment (figure 2). This difference is not clinically relevant.
Two studies in the systematic review reported on maximal intraoperative HR (figure 3).

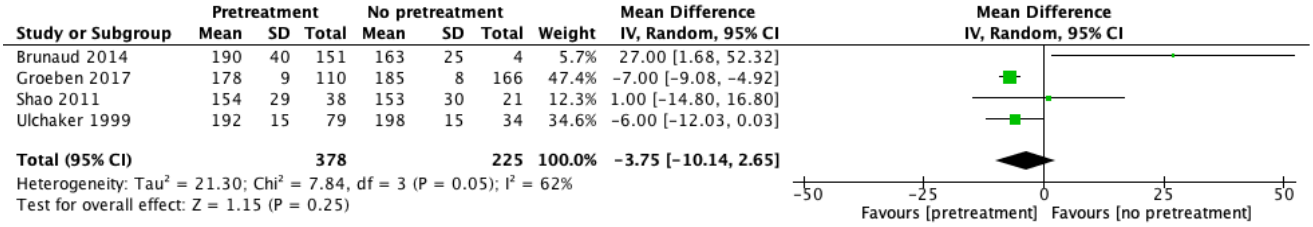


Figure 1. Outcome maximal intraoperative systolic blood pressure (mmHg) with pretreatment versus no pretreatment
Z: p-value of pooled effect; df: degrees of freedom, I2: statistical heterogeneity, CI: confidence interval

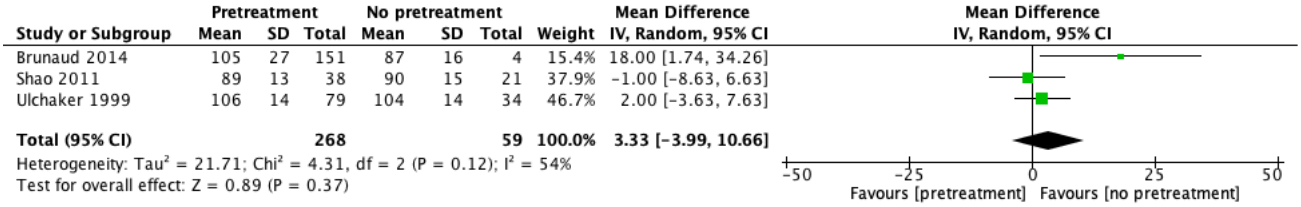


Figure 2. Outcome maximal intraoperative diastolic blood pressure (mmHg) with pretreatment versus no pretreatment
Z: p-value of pooled effect; df: degrees of freedom, I2: statistical heterogeneity, CI: confidence interval

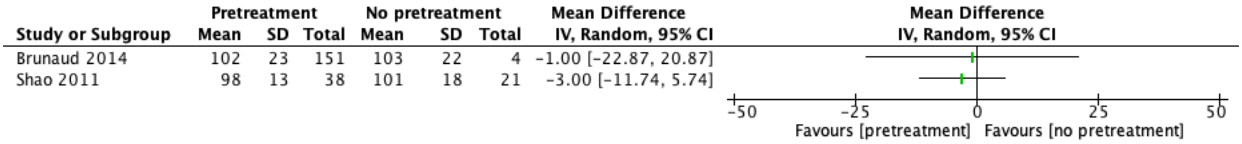


Figure 3. Outcome maximal intraoperative heart rate (bpm) with pretreatment versus no pretreatment

Level of evidence of the literature

The level of evidence of observational cohort studies is considered low according to the GRADE methodology. Therefore, the level of evidence of these cohort studies starts at low GRADE.

Mortality

The level of evidence regarding the outcome measure **mortality** was downgraded by three levels because of disproportionate group sizes and study limitations (-2; risk of bias, mainly regarding confounding) and small number of events (-1; imprecision). The level of evidence was therefore graded as very low.

Cardiovascular complications

The level of evidence regarding the outcome measure **cardiovascular complications** was downgraded by two levels because of study limitations (-1; risk of bias, mainly regarding confounding) and small number of included patients (-1; imprecision). The level of evidence was therefore graded as very low.

Length of stay

The level of evidence regarding the outcome measure **length of stay** was downgraded by two levels because of study limitations (-1; risk of bias, mainly regarding confounding) and small number of included patients (-1; imprecision). The level of evidence was therefore graded as very low.

Duration of hemodynamic support

Because **duration of hemodynamic support** was not reported by any of the included studies, level of evidence of this outcome was not rated.

Hemodynamic stability

The level of evidence regarding the outcome measure **hemodynamic stability** was downgraded by two levels because of study limitations (-1; risk of bias, mainly regarding confounding) and conflicting results (-1; inconsistency). The level of evidence was therefore graded as very low.

Conclusions

Mortality

Very low GRADE	The evidence is very uncertain about the effect of pretreatment for blood pressure on mortality when compared to no pretreatment for blood pressure in patients undergoing surgery for their pheochromocytoma. *Source: Brunaud, 2014; Buscemi, 2021; Groeben, 2020; Ulchaker, 1999*

Cardiovascular complications

Very low GRADE	The evidence is very uncertain about the effect of pretreatment for blood pressure on cardiovascular complications when compared to no pretreatment

	for blood pressure in patients undergoing surgery for their pheochromocytoma. *Source: Buscemi, 2021; Groeben, 2017; Groeben, 2020; Ulchaker, 1999*

Length of stay

Very low GRADE	The evidence is very uncertain about the effect of pretreatment for blood pressure on length of stay when compared to no pretreatment for blood pressure in patients undergoing surgery for their pheochromocytoma. *Source: Buscemi, 2021*

Duration of hemodynamic support

- GRADE	No evidence was found regarding the effect of pretreatment for blood pressure on duration of hemodynamic support when compared to no pretreatment for blood pressure in patients undergoing surgery for their pheochromocytoma. *Source: -*

Hemodynamic stability

Very low GRADE	The evidence is very uncertain about the effect of pretreatment for blood pressure on hemodynamic stability when compared to no pretreatment for blood pressure in patients undergoing surgery for their pheochromocytoma. *Source: Brunaud, 2014; Groeben, 2017; Shao, 2011; Ulchaker, 1999*

Overwegingen – van bewijs naar aanbeveling

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

De werkgroep heeft een literatuuronderzoek verricht naar de effecten van voorbehandeling van bloeddruk vergeleken met geen voorbehandeling in patiënten die geopereerd zullen worden aan hun feochromocytoom. Resultaten voor beide cruciale uitkomstmaten (mortaliteit en cardiovasculaire complicaties) werden gerapporteerd in de geïncludeerde studies. Één studie rapporteerde de 30-dagenmortaliteit en drie studies rapporteerden de perioperatieve mortaliteit. In slechts één van deze studies kwam er perioperatieve sterfte voor. Deze was 0.2% hoger in de groep met alfa-blokkade voorbehandeling dan in de groep zonder voorbehandeling. Dit verschil is niet klinisch relevant. Vier studies rapporteerden cardiovasculaire complicaties. In twee studies waren er geen cardiovasculaire complicaties in beide groepen. In de andere twee studies waren er meer cardiovasculaire complicaties in de groep met bloeddruk voorbehandeling dan in de groep zonder voorbehandeling. Deze verschillen zijn klinisch relevant.

Voor twee van de drie belangrijke uitkomstmaten (ligduur en hemodynamische stabiliteit) werden resultaten gerapporteerd in de geïncludeerde studies. Ligduur werd in één studie gerapporteerd. Hemodynamische stabiliteit werd door vier studies beschreven aan de hand van maximale intraoperatieve systolische bloeddruk, maximale intraoperatieve diastolische bloeddruk en/of maximale intraoperatieve hartslag. Deze resultaten lieten geen duidelijke richting zien in het voordeel van voorbehandeling of geen voorbehandeling. Duur van hemodynamische ondersteuning werd niet gerapporteerd in de geïncludeerde studies.

De bewijskracht is voor alle uitkomstmaten zeer laag, waarmee de overall bewijskracht ook zeer laag is. Dit heeft verschillende redenen. Ten eerste hebben alle geïncludeerde studies een observationeel design. Daarnaast hebben de studies niet gecorrigeerd voor mogelijke confounders, wat het risico op bias beïnvloedt. (Nor)metanefrine concentratie, tumorgrootte en bloeddruk bij baseline werden niet in alle studies gerapporteerd en waren in sommige gevallen niet vergelijkbaar in de groep met en de groep zonder voorbehandeling. Als risicofactoren voor intraoperatieve hypertensie (Bruynzeel, 2010), kan dit de resultaten beïnvloed hebben. Bovendien waren er verschillen in de soort preoperatieve blokkade. Zeer waarschijnlijk is er ook sprake van selectiebias: in de studies wordt niet beschreven welke patiënten preoperatieve voorbehandeling kregen en waar deze keuze op gebaseerd werd. Tot slot waren de patiëntenaantallen klein en waren er grote verschillen in groepsgrootte binnen de studies.

Op basis van de cruciale uitkomstmaten kan er geen eenduidig besluit genomen worden over de waarde van preoperatieve blokkade bij patiënten met feochromocytoom. Uit de literatuursamenvatting kan er vanwege de zeer lage bewijskracht geen conclusie getrokken worden.

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

De toegevoegde waarde van voorbehandeling met alfablokkade is op basis van de gevonden studies niet aangetoond. Internationale richtlijnen adviseren dit wel (Endocrine Society Clinical Practice Guideline 2014, North American Neuroendocrine Tumor Society 2010) om cardiovasculaire complicaties te voorkomen en in de meeste Nederlandse centra is voorbehandeling dan ook de standaard behandeling (van der Horst 2006). De mortaliteit en het complicatiesrisico van een feochromocytoomresectie is de afgelopen decennia sterk gedaald (voorheen omstreeks 25% mortaliteit (Schimmack) heden mortaliteit <0,5% en cardiovasculaire complicaties 0-5,9%, zie geselecteerde studies). Sinds halverwege de 20e eeuw is de preoperatieve alfablokkade geintroduceerd, maar zijn er ook verbeterde operatietechnieken, zijn er minder infecties en is er betere anesthesiologische zorg zoals continue hemodynamische bewaking en zijn er kortwerkende bloeddrukverlagende middelen beschikbaar. Feochromocytomen worden ook eerder ontdekt doordat patiënten gemonitord worden (bij bekende genmutaties) of ze worden eerder per toeval ontdekt als incidentaloom.

De werkgroep vindt dat de keuze wel of geen voorbehandeling voornamelijk op basis van expertise van het behandelend team moet zijn. Aanvullende argumenten voor preoperatieve alfablokkade zouden kunnen zijn dat er grote hemodynamische schommelingen verwacht worden en daardoor mogelijke complicaties zoals bij een groot feochromocytoom, hoge hormoonproductie van de tumor of een hoge mate van hypertensie (Ma 2020, Araujo-Castro 2021), of dat een patiënt minimale schommelingen niet zou kunnen verdragen (bijvoorbeeld bij bekende aneurysmata).
Indien er voorbehandeld wordt met alfablokkade, dan is dit voor sommige patiënten (gedeeltelijk) in thuisbehandeling mogelijk, onder monitoring van de endocrinoloog. Dit zou door patiënten als comfortabeler kunnen worden ervaren. Voorwaarde is dat de patiënt zelf goed de bloeddruk kan meten, de mogelijke bijwerkingen begrijpt, instructies uit kan voeren en weet wanneer er contact gelegd moet worden met de endocrinoloog. Wanneer er sprake is van hypertensie of andere catecholamine-gerelateerde symptomen of bij eerder doorgemaakte cardiovasculaire complicaties, dan adviseert de werkgroep deze wel te behandelen en te controleren in de periode tot de operatie met als 1^{e} keuze een alfablokker.

Kosten (middelenbeslag)
Wanneer van voorbehandeling wordt afgezien, dan bespaart dit de kosten van een opname van 1-2 weken inclusief personeel, de medicatie en monitoring. Indien voorbehandeling poliklinisch wordt uitgevoerd dan worden de kosten van de opname bespaard.

Voorbehandeling zou postoperatief nog consequenties kunnen hebben zoals een langere opnameduur op een bewaakte afdeling of in het ziekenhuis. De ervaring is dat onvoorbereide mensen sneller naar een onbewaakte afdeling kunnen, omdat zij minder lang hemodynamisch ondersteunt hoeven te worden.

Aanvaardbaarheid, haalbaarheid en implementatie
In de meeste centra in Nederland wordt momenteel voorbehandeld, waardoor hierin ook de meeste expertise is. Dit kan een goed argument zijn om dit zo voor te zetten. Ervoor kiezen om niet iedere patiënt voor te behandelen zou dan multidisciplinair besproken kunnen worden, tenminste in samenspraak met de endocrinoloog, chirurg en anesthesioloog.

Aanbevelingen
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Op basis van de beschikbare literatuur kan voorbehandeling met alfablokkade niet worden geadviseerd, maar ook niet worden afgeraden. In de meeste Nederlandse ziekenhuizen is voorbehandeling standaard en is er geen expertise voor feochromocytoomresecties bij ongeblokte patiënten. Deze expertise in het team weegt het zwaarst, daarom kiest de werkgroep voor deze aanbeveling, ondanks het gebrek aan bewijs, de belasting voor de patiënt en de kosten. Er wordt aanbevolen om te overwegen of een klinische opname in het geval van voorbehandeling noodzakelijk is.

Behandel een patiënt voor een feochromocytoomresectie voor met alfablokkade, indien dit in het expertisecentrum gebruikelijk is.

Overweeg patiënten *klinisch* voor te behandelen indien ze:
- Niet zelfstandig bloeddruk kunnen meten,
- Geen instructies kunnen volgen en/of
- Niet therapietrouw worden geacht.

Overweeg het afzien van voorbehandeling voor een feochromocytoomresectie op basis van expertise van het behandelteam, patiëntfactoren en afwezige risicofactoren voor hemodynamische veranderingen peroperatief zoals:
- kleinere tumoren, al dan niet incidentalomen
- pre-operatief goed gecontroleerde bloeddruk
- licht verhoogde catecholamine productie.

Literatuur
Araujo-Castro M, Garcia Centeno R, López-García MC, Lamas C, Álvarez-Escolá C, Calatayud Gutiérrez M, Blanco-Carrera C, de Miguel Novoa P, Valdés N, Gracia Gimeno P, Fernández-Ladreda MT, Mínguez Ojeda C, Percovich Hualpa JC, Mora M, Vidal Ó, Serrano Romero A, Hanzu FA, Gómez Dos Santos V. Risk factors for intraoperative complications in pheochromocytomas. Endocr Relat Cancer. 2021 Sep 8;28(11):695-703. doi: 10.1530/ERC-21-0230. PMID: 34379605.

Brunaud L, Boutami M, Nguyen-Thi PL, Finnerty B, Germain A, Weryha G, Fahey TJ 3rd, Mirallie E, Bresler L, Zarnegar R. Both preoperative alpha and calcium channel blockade

impact intraoperative hemodynamic stability similarly in the management of pheochromocytoma. Surgery. 2014 Dec;156(6):1410-7; discussion1417-8. doi: 10.1016/j.surg.2014.08.022. Epub 2014 Nov 11. PMID: 25456922.

Bruynzeel H, Feelders RA, Groenland TH, van den Meiracker AH, van Eijck CH, Lange JF, de Herder WW, Kazemier G. Risk Factors for Hemodynamic Instability during Surgery for Pheochromocytoma. J Clin Endocrinol Metab. 2010 Feb;95(2):678-85. doi: 10.1210/jc.2009-1051. Epub 2009 Dec 4. PMID: 19965926.

Buscemi S, Di Buono G, D'Andrea R, Ricci C, Alberici L, Querci L, Selva S, Minni F, Citarrella R, Romano G, Agrusa A. Perioperative Management of Pheochromocytoma: From a Dogmatic to a Tailored Approach. J Clin Med. 2021 Aug 23;10(16):3759. doi: 10.3390/jcm10163759. PMID: 34442056; PMCID: PMC8397195.

Groeben H, Nottebaum BJ, Alesina PF, Traut A, Neumann HP, Walz MK. Perioperative α-receptor blockade in phaeochromocytoma surgery: an observational case series. Br J Anaesth. 2017 Feb;118(2):182-189. doi: 10.1093/bja/aew392. PMID: 28100521.

Groeben H, Walz MK, Nottebaum BJ, Alesina PF, Greenwald A, Schumann R, Hollmann MW, Schwarte L, Behrends M, Rössel T, Groeben C, Schäfer M, Lowery A, Hirata N, Yamakage M, Miller JA, Cherry TJ, Nelson A, Solorzano CC, Gigliotti B, Wang TS, Wietasch JKG, Friederich P, Sheppard B, Graham PH, Weingarten TN, Sprung J. International multicentre review of perioperative management and outcome for catecholamine-producing tumours. Br J Surg. 2020 Jan;107(2):e170-e178. doi: 10.1002/bjs.11378. PMID: 31903598; PMCID: PMC8046358.

Ma L, Shen L, Zhang X, Huang Y. Predictors of hemodynamic instability in patients with pheochromocytoma and paraganglioma. J Surg Oncol. 2020 Jun 20;122(4):803–8. doi: 10.1002/jso.26079.

Schimmack S, Kaiser J, Probst P, Kalkum E, Diener MK, Strobel O. Meta-analysis of α-blockade versus no blockade before adrenalectomy for phaeochromocytoma. Br J Surg. 2020 Jan;107(2):e102-e108. doi: 10.1002/bjs.11348. PMID: 31903584.

Shao Y, Chen R, Shen ZJ, Teng Y, Huang P, Rui WB, Xie X, Zhou WL. Preoperative alpha blockade for normotensive pheochromocytoma: is it necessary? J Hypertens. 2011 Dec;29(12):2429-32. doi: 10.1097/HJH.0b013e32834d24d9. PMID: 22025238.

Ulchaker JC, Goldfarb DA, Bravo EL, Novick AC. Successful outcomes in pheochromocytoma surgery in the modern era. J Urol. 1999 Mar;161(3):764-7. PMID: 10022680.

Van der Horst-Schrivers AN, Kerstens MN, Wolffenbuttel BH. Preoperative pharmacological management of phaeochromocytoma. Neth J Med. 2006 Sep;64(8):290-5. PMID: 16990692

Bijlagen bij module Behandeling feochromocytoom

Evidence tables

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

Research question: What are the (un)favorable effects of pretreatment for blood pressure versus no pretreatment in patients undergoing surgery for pheochromocytoma on mortality, cardiovascular complications, length of stay and hemodynamic parameters?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Schimmack, 2020	SR and meta-analysis of 4 observational studies *Literature search up to November 2018* **A**: Ulchaker, 1999 **B**: Shao, 2011 **C**: Brunaud, 2014 **D**: Groeben, 2017 Study design: Retrospective cohort **(A,B,C)** and case series **(D)** Setting and Country: **A:** 1 institution, USA **B:** 1 institution,	Inclusion criteria SR: - RCTs or non-randomized controlled studies - comparing preoperative α-blockade with no blockade in phaeochromocytoma surgery in adults Exclusion criteria SR: - evaluating exclusively medical treatment other than α-blockers - full text not available *4 studies included* Important patient characteristics at baseline:	**A**: preoperative α blockade (selective/non-selective) with calcium channel blocker/beta-blocker if needed (mixed treatment) **B**: preoperative α_1-blockade doxazosin (selective) **C**: preoperative α-blockade with phenoxybenzamine (non-selective) **D**: preoperative α-receptor blockade with phenoxy-benzamine (non-selective) or doxazosin (selective)	**A**: no preoperative α blockade, calcium channel blocker/beta-blocker if needed **B**: no preoperative α-adrenoceptor **C**: perioperative calcium channel blockade (nicardipine regimen) or no medication **D**: no α-receptor blockade	End-point of follow-up: **A**: not stated **B**: not stated **C**: not stated **D**: not stated For how many participants were no complete outcome data available? **A:** not stated **B**: not stated **C**: not stated (but patients with incomplete medical records were excluded) **D**: not stated	Effect on mortality, cardiovascular complications and hemodynamic parameters Mortality **A:** I: 0/79, C: 0/34 patients **B:** not reported **C:** I: 0/151, C: 0/4 patients **D:** not reported Not meta-analysed (too few data or events) Cardiovascular complications **A:** I: 6/79, C: 0/34 patients **B:** I: 0/38, C: 0/21 patients **C:** not reported **D:** I: 0/110, C: 0/166 patients Not meta-analysed (too few data or events)	Author's conclusion: There is no evidence supporting preoperative α-blockade before adrenalectomy for phaeochromocytoma as recommended in current guidelines. The level of evidence is too low to conclude that the practice of preoperative α-blockade can safely be abandoned. RCTs are needed to generate the evidence needed on this topic.

	China **C:** 3 institutions, France and USA **D:** 1 institution, Germany <u>Source of funding and conflicts of interest:</u> **A:** Unclear **B:** No conflicts of interest **C:** Unclear **D:** Supported solely by institutional and departmental sources, no conflicts of interest	<u>*N total at baseline*</u> **A**: Intervention: 79 Control: 34 **B**: Intervention: 38 Control: 21 **C**: Intervention: 151 Control: 4 **D:** Intervention: 110 Control: 166 <u>*Age±SD or (range):*</u> **A:** total: 44 (14-84) **B:** I: 43±11, C: 38±12 **C:** total: 52±15 **D:** I: 43 (18-82), C: 43 (18-79) <u>*Sex:*</u> **A**: total: 47% M **B**: I: 45% M, C: 43% M **C**: I: 44% M, C: 50% M **D:** I: 58% M, C: 46% M <u>*Phaeochromocytoma*</u> **A:** (extra-)adrenal, uni-/bilateral **B:** adrenal, unilateral **C:** adrenal, unilateral **D:** (extra-)adrenal, uni-/bilateral <u>*Tumor size±SD or (range) (cm)*</u> **A:** total: 6 (1.8-22) **B:** I: 5.5±2.3, C: 5.7±4.2 **C:** total: 4.5±2.0				<u>Mean maximal intraoperative systolic blood pressure</u> *I minus C (mmHg), mean difference [95%CI]* **A**: -6.00 [-12.03, 0.03] **B**: 1.00 (-14.80, 16.80] **C:** 27.00 [1.68, 52.32] **D**: -7.00 [-9.08, -4.92] <u>Mean maximal intraoperative diastolic blood pressure</u> *I minus C (mmHg), mean difference [95%CI]* **A:** 2.00 [-3.63, 7.63] **B:** -1.00 [-8.63, 6.63] **C:** 18.00 [1.74, 34.26] **D:** not reported <u>Mean maximal intraoperative heart rate</u> *I minus C (bpm), mean difference [95%CI]* **A:** not reported **B:** -3.00 [-11.74, 5.74] **C:** -1.00 [-22.87, 20.87] **D:** not reported	

		D: I: 3.8 (3.4-4.2), C: 3.4 (3.1-3.7) Groups comparable at baseline? No					

Evidence table for intervention studies

Research question: What are the (un)favorable effects of pretreatment for blood pressure versus no pretreatment in patients undergoing surgery for pheochromocytoma on mortality, cardiovascular complications, length of stay and hemodynamic parameters?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Buscemi, 2021	Type of study: bicentric retrospective case-control study Setting and country: two University Hospitals in Italy Funding and conflicts of interest: no external funding, no conflict of interest	Inclusion criteria: - patients undergoing laparoscopic adrenalectomy for pheochromocytoma from 2000 to 2017 - preoperative positive catecholamine test with high levels of plasma-free metanephrines or 24 h urinary fractionated metanephrine - final pathological diagnosis of phaechromocytoma Exclusion criteria:	Preoperative alpha-blockade, non-selectively with phenoxybenzamine (n=37), or selectively with doxazosin (n=12). Patients treated with phenoxybenzamine were encouraged to take a preoperative high-sodium diet and fluid intake. A beta-blocker was added in cases of tachycardia.	No preoperative alpha-blockade but only miscellaneous, on-demand, antihypertensive drugs during the crisis. Chronic cardiovascular therapy was continued.	Follow-up: Not described. Incomplete outcome data: One centre could not provide data on partial resections, one could not specify the type of preoperative α-receptor blockade used, four centres were unable to determine the frequency of episodes with an intraoperative systolic BP above 250 mmHg, and two could not provide the number of patients requiring postoperative treatment in the ICU.	Mortality I: 0/49 patients C: 0/14 patients Perioperative cardiovascular complications I: 0/49 patients C: 0/14 patients Length of stay (median (IQR)) I: 5 days (4-6) C: 4 days (4-4) p=0.03	Author's conclusion: The preoperative use of alfa-blockers should be considered not a dogma in PCC.

		- planned open and bilateral adrenalectomies - missing anesthetic records N total at baseline: Intervention: 49 Control: 14 Important prognostic factors[2]: *Age (median (IQR)):* *I: 56.00 (49.00-70.25)* *C: 57.00 (44.00-70.00)* *Sex:* *I: 47% M* *C: 29% M* *Tumor size (median (IQR)) (cm):* *I: 3.2 (2.38-8.70)* *C: 4.5 (3.63-5.88)* Groups comparable at baseline? No					
Groeben, 2020	Type of study: retrospective cohort study Setting and country: Centres from six countries (Australia, Germany,	Inclusion criteria: patients who had surgery for phaeochro-mocytoma or paraganglioma between 2000 and 2017 Exclusion criteria:	Preoperative α-receptor blockade (predominantly phenoxybenzamine, followed by doxazosin, prazosin and terazosin) (selective or non-selective).	No α-receptor blockade.	Follow-up: Not described. Incomplete outcome data: One centre could not provide data on partial resections, one could not specify the type of preoperative α-receptor blockade used, four	Mortality (perioperative) I: 0.5% (95% CI 0.1 to 0.9) (8/1517 patients) C: 0.3% (95% CI 0.3 to 0.9) (1/343 patients) p=0.569 Cardiovascular complications I: 5.9% (90/1517 patients)	Author's conclusion: There is substantial variability in the perioperative management of catecholamine- producing tumours, yet the overall complication rate is low. Further studies are needed to better define the optimal management approach, and

	Ireland, Japan, the Netherlands, USA) Funding and conflicts of interest: no conflict of interest, no information on funding	no histologically verified tumour <u>N total at baseline</u>: Intervention: 1517 Control: 343 <u>Important prognostic factors</u>[2] Only reported for the centre with the largest group of patients without α-receptor blockade (n=504). In this centre, the groups were comparable at baseline regarding age, sex ratio and tumor diameter.			centres were unable to determine the frequency of episodes with an intraoperative systolic BP above 250 mmHg, and two could not provide the number of patients requiring postoperative treatment in the ICU.	C: 0.9% (95% CI -0.1 to 1.9) (3/343 patients) p<0.001	reappraisal of international perioperative guidelines appears desirable.

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

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

Research question: What are the (un)favorable effects of pretreatment for blood pressure versus no pretreatment in patients undergoing surgery for pheochromocytoma on mortality, cardiovascular complications, length of stay and hemodynamic parameters?

Study **First author, year**	**Appropriate and clearly focused question?[1]** **Yes/no/unclear**	**Comprehensive and systematic literature search?[2]** **Yes/no/unclear**	**Description of included and excluded studies?[3]** **Yes/no/unclear**	**Description of relevant characteristics of included studies?[4]** **Yes/no/unclear**	**Appropriate adjustment for potential confounders in observational studies?[5]** **Yes/no/unclear/not applicable**	**Assessment of scientific quality of included studies?[6]** **Yes/no/unclear**	**Enough similarities between studies to make combining them reasonable?[7]** **Yes/no/unclear**	**Potential risk of publication bias taken into account?[8]** **Yes/no/unclear**	**Potential conflicts of interest reported?[9]** **Yes/no/unclear**
Schimmack, 2020	Yes, but the research question and inclusion criteria could have been defined more explicitly.	Yes, the full search strategies for all databases are provided in the appendix and the date of the last search is mentioned.	No, the only given reason for the records excluded after full-text screening is 'wrong intervention'.	No, only a few characteristics are described. Important characteristics are missed (e.g. age).	No, confounding was not mentioned, nor addressed in the systematic review and in the separate observational studies.	Yes, the methodological quality was assessed using the ROBINS-I tool.	Yes, the studies have similarities, although one can doubt the different combinations of preoperative treatment and different types of phaeochromocytomas (extra-adrenal, bilateral). Statistical heterogeneity was evaluated using the I^2 statistic.	Yes, it is mentioned that no funnel plots were created as only four non-randomized studies were included.	No, the authors of the systematic review declare no conflict of interest, but support or conflicts of interest were not mentioned in two included studies (Brunaud, Ulchaker).

1. Research question (PICO) and inclusion criteria should be appropriate and predefined
2. Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched
3. Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons
4. Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported
5. Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)
6. Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)
7. Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I^2)?
8. An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
9. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.

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

Research question: What are the (un)favorable effects of pretreatment for blood pressure versus no pretreatment in patients undergoing surgery for pheochromocytoma on mortality, cardiovascular complications, length of stay and hemodynamic parameters?

Author, year	Selection of participants Was selection of exposed and non-exposed cohorts drawn from the same population?	Exposure Can we be confident in the assessment of exposure?	Outcome of interest Can we be confident that the outcome of interest was not present at start of study?	Confounding-assessment Can we be confident in the assessment of confounding factors?	Confounding-analysis Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?	Assessment of outcome Can we be confident in the assessment of outcome?	Follow up Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?	Co-interventions Were co-interventions similar between groups?	Overall Risk of bias
	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Low, Some concerns, High
Buscemi, 2021	Probably yes Reason: patients undergoing laparoscopic adrenalectomy for	Probably yes Reason: both institutions collected data of patients in a prospectively maintained	Definitely yes Reason: patients were preoperatively treated with alpha-blockade.	**Probably no** Reason: it is not described in the methods which confounders were assessed.	**Probably no** Reason: one of the analyses was multivariate, but the statistical methods were not described. The	**Probably no** Reason: no complete information on the definition and collection	No information Reason: no follow-up duration mentioned.	Probably yes Reason: some patients in the alpha-blockade group also received beta-blockers and/or	**High (all outcomes)**

	pheochromocytoma in one of the two centers from 2000 to 2017 were included.	adrenal database.			tumor size, as mentioned in the discussion, was not included in the analyses.	of the outcomes.		calcium channel blockers. This is part of the preoperative anti-hypertensive management.	
Groeben, 2020	Definitely yes Reason: participants were selected from an international multicentre retrospective database.	Probably yes Reason: all centres could provide data on the preoperative blockade.	Definitely yes Reason: patients were preoperatively treated with alpha-blockade.	**Probably no** Reason: it is not described in the methods which confounders were assessed.	**Definitely no** Reason: an analysis for confounding variables was not undertaken owing to the small fraction and type of data that each individual centre was able to contribute to the data set.	Probably yes Reason: the outcome data was provided by the centres. Missing data was roughly balanced.	Probably yes Reason: follow-up of 3 months was sufficient for the outcome postoperative mortality.	Probably yes Reason: additional used medication seems balanced between groups.	**Some concerns (all outcomes)**

Table of excluded studies

Reference	Reason for exclusion
Araujo-Castro M, Garcia Centeno R, López-García MC, Lamas C, Álvarez-Escolá C, Calatayud Gutiérrez M, Blanco-Carrera C, de Miguel Novoa P, Valdés N, Gracia Gimeno P, Fernández-Ladreda MT, Mínguez Ojeda C, Percovich Hualpa JC, Mora M, Vidal Ó, Serrano Romero A, Hanzu FA, Gómez Dos Santos V. Risk factors for intraoperative complications in pheochromocytomas. Endocr Relat Cancer. 2021 Sep 8;28(11):695-703. doi: 10.1530/ERC-21-0230. PMID: 34379605.	Wrong study design (identification of presurgical and surgical risk factors for intraoperative complications)
Araujo-Castro M, García Centero R, López-García MC, Álvarez Escolá C, Calatayud Gutiérrez M, Blanco Carrera C, De Miguel Novoa P, Valdés Gallego N, Hanzu FA, Gracia Gimeno P, Fernández-Ladreda MT, Percovich Hualpa JC, Mora Porta M, Lorca Álvaro J, Pian H, Caracuel IR, Sanjuanbenito Dehesa A, Gómez Dos Santos V, Serrano Romero A, Oliveira CL. Surgical outcomes in the pheochromocytoma surgery. Results from the PHEO-RISK STUDY. Endocrine. 2021 Dec;74(3):676-684. doi: 10.1007/s12020-021-02843-6. Epub 2021 Aug 9. PMID: 34373995.	Wrong comparison (selective vs. non-selective alpha-blockade)
Bruynzeel H, Feelders RA, Groenland TH, van den Meiracker AH, van Eijck CH, Lange JF, de Herder WW, Kazemier G. Risk Factors for Hemodynamic Instability during Surgery for Pheochromocytoma. J Clin Endocrinol Metab. 2010 Feb;95(2):678-85. doi: 10.1210/jc.2009-1051. Epub 2009 Dec 4. PMID: 19965926.	Wrong comparison (selective vs. non-selective alpha-blockade)
Buisset C, Guerin C, Cungi PJ, Gardette M, Paladino NC, Taïeb D, Cuny T, Castinetti F, Sebag F. Pheochromocytoma surgery without systematic preoperative pharmacological preparation: insights from a referral tertiary center experience. Surg Endosc. 2021 Feb;35(2):728-735. doi: 10.1007/s00464-020-07439-1. Epub 2020 Feb 18. PMID: 32072283.	Wrong study design (identification of the predictive factors of global and cardiovascular morbidity)
Buitenwerf E, Osinga TE, Timmers HJLM, Lenders JWM, Feelders RA, Eekhoff EMW, Haak HR, Corssmit EPM, Bisschop PHLT, Valk GD, Veldman RG, Dullaart RPF, Links TP, Voogd MF, Wietasch GJKG, Kerstens MN. Efficacy of α-Blockers on Hemodynamic Control during Pheochromocytoma Resection: A Randomized Controlled Trial. J Clin Endocrinol Metab. 2020 Jul 1;105(7):2381–91. doi: 10.1210/clinem/dgz188. PMID: 31714582; PMCID: PMC7261201.	Wrong comparison (selective vs. non-selective alpha-blockade)
Conzo G, Musella M, Corcione F, Depalma M, Stanzione F, Della-Pietra C, Palazzo A, Napolitano S, Pasquali D, Milone M, Agostino-Sinisi A, Ferraro F, Santini L. Role of preoperative adrenergic blockade	Wrong intervention (all participants received alpha-blockade)

with doxazosin on hemodynamic control during the surgical treatment of pheochromocytoma: a retrospective study of 48 cases. Am Surg. 2013 Nov;79(11):1196-202. PMID: 24165257.	
FAN, H., LI, H., JI, Z., ZHANG, X., WEN, J., XU, W., & ZHANG, Y. (2019). Analysis of clinical characteristics for hypertensive attack during pheochromocytoma and paraganglioma operation: a single center case report of 219 cases. Chinese Journal of Urology, 267-271.	Article in Chinese
Groeben H. Präoperative α-Rezeptoren-Blockade beim Phäochromozytom? - Kontra [Preoperative α-receptor block in patients with pheochromocytoma? Against]. Chirurg. 2012 Jun;83(6):551-4. German. doi: 10.1007/s00104-011-2196-3. PMID: 22437284.	Article in German
Groeben H, Nottebaum BJ, Alesina PF, Traut A, Neumann HP, Walz MK. Perioperative α-receptor blockade in phaeochromocytoma surgery: an observational case series. Br J Anaesth. 2017 Feb;118(2):182-189. doi: 10.1093/bja/aew392. PMID: 28100521.	Included in systematic review from Schimmack
Kwon SY, Lee KS, Lee JN, Ha YS, Choi SH, Kim HT, Kim TH, Yoo ES, Kwon TG. Risk factors for hypertensive attack during pheochromocytoma resection. Investig Clin Urol. 2016 May;57(3):184-90. doi: 10.4111/icu.2016.57.3.184. Epub 2016 May 2. PMID: 27194549; PMCID: PMC4869566.	Wrong study design (identification of risk factors for hypertensive attack)
Lafont M, Fagour C, Haissaguerre M, Darancette G, Wagner T, Corcuff JB, Tabarin A. Per-operative hemodynamic instability in normotensive patients with incidentally discovered pheochromocytomas. J Clin Endocrinol Metab. 2015 Feb;100(2):417-21. doi: 10.1210/jc.2014-2998. Epub 2014 Nov 18. PMID: 25405501.	Wrong comparison (normotensive pheochromocytomas, hypertensive pheochromocytomas, and benign nonpheochromocytoma adrenal incidentalomas)
Li J, Yang CH. Improvement of preoperative management in patients with adrenal pheochromocytoma. Int J Clin Exp Med. 2014 Dec 15;7(12):5541-6. PMID: 25664068; PMCID: PMC4307515.	Wrong comparison (selective vs. non-selective alpha-blockade)
Liu H, Li B, Yu X, Huang Y. Perioperative management during laparoscopic resection of large pheochromocytomas: A single-institution retrospective study. J Surg Oncol. 2018 Sep;118(4):709-715. doi: 10.1002/jso.25205. Epub 2018 Sep 2. PMID: 30175399.	Wrong study design (correlation between tumor size and perioperative characteristics)
Livingstone M, Duttchen K, Thompson J, Sunderani Z, Hawboldt G, Sarah Rose M, Pasieka J. Hemodynamic Stability During Pheochromocytoma Resection: Lessons Learned Over the Last Two Decades. Ann Surg Oncol. 2015 Dec;22(13):4175-80. doi:	Wrong study design (identification of predictors of hemodynamic instability)

10.1245/s10434-015-4519-y. Epub 2015 Mar 31. PMID: 25822781.	
Ma L, Shen L, Zhang X, Huang Y. Predictors of hemodynamic instability in patients with pheochromocytoma and paraganglioma. J Surg Oncol. 2020 Jun 20;122(4):803–8. doi: 10.1002/jso.26079. Epub ahead of print. PMID: 32562589; PMCID: PMC7496938.	Wrong study design (identification of risk factors for intraoperative hemodynamic instability)
Malec K, Miśkiewicz P, Witkowska A, Krajewska E, Toutounchi S, Gałązka Z, Piotrowski M, Kącka A, Bednarczuk T, Ambroziak U. Comparison of phenoxybenzamine and doxazosin in perioperative management of patients with pheochromocytoma. Kardiol Pol. 2017;75(11):1192-1198. doi: 10.5603/KP.a2017.0147. Epub 2017 Jul 17. PMID: 28715066.	Wrong comparison (selective vs. non-selective alpha-blockade)
Miyamoto S, Yoshida Y, Ozeki Y, Okamoto M, Gotoh K, Masaki T, Nishida H, Shibuya T, Shin T, Daa T, Mimata H, Kimura N, Shibata H. Dopamine-Secreting Pheochromocytoma and Paraganglioma. J Endocr Soc. 2021 Oct 29;5(12):bvab163. doi: 10.1210/jendso/bvab163. PMID: 34870059; PMCID: PMC8633142.	Narrative review
Prys-Roberts C, Farndon JR. Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. World J Surg. 2002 Aug;26(8):1037-42. doi: 10.1007/s00268-002-6667-z. Epub 2002 Jun 19. PMID: 12192533.	Wrong comparison (selective vs. non-selective alpha-blockade)
Sergiĭko SV, Privalov VA. [The influence of preoperative preparation on changes in haemodynamics in patients with pheochromocytoma]. Vestn Khir Im I I Grek. 2010;169(1):80-4. Russian. PMID: 20387613.	Article in Russian
Shao Y, Chen R, Shen ZJ, Teng Y, Huang P, Rui WB, Xie X, Zhou WL. Preoperative alpha blockade for normotensive pheochromocytoma: is it necessary? J Hypertens. 2011 Dec;29(12):2429-32. doi: 10.1097/HJH.0b013e32834d24d9. PMID: 22025238.	Included in systematic review from Schimmack
Shu Q, Lan L, Zhang Y, Yu C, Huang Y. Predictors of prolonged hypotension requiring vasopressor support after resection of pheochromocytoma and paraganglioma. Clin Endocrinol (Oxf). 2021 Dec;95(6):841-848. doi: 10.1111/cen.14542. Epub 2021 Jul 12. PMID: 34160851.	Wrong study design (identification of predictors of postoperative hypotension)
van der Horst-Schrivers AN, Kerstens MN, Wolffenbuttel BH. Preoperative pharmacological management of phaeochromocytoma. Neth J Med. 2006 Sep;64(8):290-5. PMID: 16990692.	Narrative review
van der Zee PA, de Boer A. Pheochromocytoma: a review on preoperative treatment with	Narrative review

phenoxybenzamine or doxazosin. Neth J Med. 2014 May;72(4):190-201. PMID: 24829175.	
Weingarten TN, Cata JP, O'Hara JF, Prybilla DJ, Pike TL, Thompson GB, Grant CS, Warner DO, Bravo E, Sprung J. Comparison of two preoperative medical management strategies for laparoscopic resection of pheochromocytoma. Urology. 2010 Aug;76(2):508.e6-11. doi: 10.1016/j.urology.2010.03.032. Epub 2010 May 23. PMID: 20546874.	Wrong comparison (selective vs. non-selective alpha-blockade)
Zawadzka K, Więckowski K, Małczak P, Wysocki M, Major P, Pędziwiatr M, Pisarska-Adamczyk M. Selective vs non-selective alpha-blockade prior to adrenalectomy for pheochromocytoma: systematic review and meta-analysis. Eur J Endocrinol. 2021 May 4;184(6):751-760. doi: 10.1530/EJE-20-1301. PMID: 33769959.	Wrong comparison (selective vs. non-selective alpha-blockade)

Literature search strategy

Algemene informatie

Richtlijn: NVvH bijniertumoren	
Uitgangsvraag: Wat zijn de gunstige en ongunstige effecten van voorbehandeling van bloeddruk (alfablokkers, bètablokkers en/of andere antihypertensiva) versus geen voorbehandeling bij patiënten die geopereerd gaan worden aan feochromocytoom op mortaliteit, morbiditeit, ligduur en duur van hemodynamische ondersteuning/bewaking?	
Database(s): Ovid/Medline, Embase	Datum: 21-2-2022, 14-3-2022
Periode: 2000-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: **14-3-2022** Premedicatie breder opgezet in Embase. Daarnaast de zoekstrategie geüpdatet. **21-2-2022** Voor deze vraag is gezocht met de volgende elementen: Pheochromocytoma EN premedicatie EN antihypertensiva De twee sleutelartikelen worden gevonden	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 21 februari 2022 met relevante zoektermen gezocht naar systematische reviews en RCTs en observationele studies over de effecten van voorbehandeling van bloeddruk bij patiënten die geopereerd gaan worden aan feochromocytoom. De literatuurzoekactie leverde 355 unieke treffers op.	

Zoekopbrengst

14-3-2022 aanvulling Embase premedicatie	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld t.o.v. Rayyan 21-2-2022**
SRs	36		10
RCTs	35		9
Observationele studies	234		80
Overig			
Totaal			**355**
21-2-2022	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs	28	6	32
RCTs	27	31	52
Observationele studies	154	50	172
Overig			
Totaal			**256**

Zoekstrategie

Embase

14-3-2022

No.	Query	Results
#46	#44 NOT #43 NOT #42 OBS	234
#45	#43 NOT #42 RCT	35
#44	#37 AND (#40 OR #41)	283
#43	#37 AND #39	45
#42	#37 AND #38 SR	36
#41	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw)	12956175

No.	Query	Results
	AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR (('or' OR 'rr') NEAR/6 ci):ab)))	
#40	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6955857
#39	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1885566
#38	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	807539
#37	#36 AND [1-1-2000]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	874
#36	#33 AND #34 AND #35	1373
#35	'premedication'/de OR 'preoperative treatment'/de OR 'preoperative period'/exp OR 'perioperative period'/exp OR premedication*:ti,ab,kw OR (((preoperative OR 'pre operative' OR perioperative OR 'peri operative' OR presurg* OR 'pre surg*') NEAR/3 (period OR treatment OR management OR care)):ti,ab,kw)	456884
#34	'antihypertensive agent'/exp OR 'alpha adrenergic receptor blocking agent'/exp OR 'doxazosin'/exp OR 'phenoxybenzamine'/exp OR 'prazosin'/exp OR 'phentolamine'/exp OR 'magnesium sulfate'/exp OR 'glyceryl trinitrate'/exp OR 'metirosine'/exp OR 'calcium channel blocking agent'/exp OR 'nifedipine'/exp OR 'amlodipine'/exp OR 'amlodipine besylate'/exp OR nifedical:ti,ab,kw OR procardia:ti,ab,kw OR amlor:ti,ab,kw OR katerzia:ti,ab,kw OR 'dihydropyridine'/exp OR antihypertensive:ti,ab,kw OR adalat:ti,ab,kw OR afeditab:ti,ab,kw OR nifediac:ti,ab,kw OR nifedipine:ti,ab,kw OR metirosine:ti,ab,kw OR nitroglycerin*:ti,ab,kw OR parzosin:ti,ab,kw OR doxazosin:ti,ab,kw OR phentolamin*:ti,ab,kw OR 'magnesium sulfate':ti,ab,kw	1206162
#33	'adrenal tumor'/exp OR 'adrenalectomy'/exp OR (('catecholamine release'/exp OR 'catecholamine'/exp) AND 'malignant neoplasm'/exp) OR 'pheochromocytoma'/exp OR phaeochromo*:ti,ab,kw OR pheochromo*:ti,ab,kw OR catecholamine:ti,ab,kw OR ((adrenal NEAR/2 (tumor* OR cancer OR neoplasm OR malignan*)):ti,ab,kw) OR adrenalectom*:ti,ab,kw	132048

21-2-2022

No.	Query	Results
#19	#17 NOT #16 NOT #15 OBS	154
#18	#16 NOT #15 RCT	27
#17	#6 AND (#9 OR #10)	192
#16	#6 AND #8	35
#15	#6 AND #7 SR	28
#14	#6 AND #13	2

No.	Query	Results
#13	#11 OR #12	3
#12	preoperative AND alpha AND blockade AND for AND normotensive AND pheochromocytoma AND sha o AND 2011	1
#11	international AND multicentre AND review AND of AND perioperative AND management AND outcom e AND for AND 'catecholamine producing' AND tumours AND groeben	2
#10	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	12899287
#9	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#8	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814
#7	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#6	#5 AND [1-1-2000]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	550
#5	#3 AND #4	892
#4	#1 AND #2	2157
#3	'antihypertensive agent'/exp OR 'alpha adrenergic receptor blocking agent'/exp OR 'doxazosin'/exp OR 'phenoxybenzamine'/exp OR 'prazosin'/exp OR 'phentolamine'/exp OR 'magnesium sulfate'/exp OR 'glyceryl trinitrate'/exp OR 'metirosine'/exp OR 'calcium channel blocking agent'/exp OR 'nifedipine'/exp OR 'amlodipine'/exp OR 'amlodipine besylate'/exp OR nifedical:ti,ab,kw	1203395

No.	Query	Results
	OR procardia:ti,ab,kw OR amlor:ti,ab,kw OR katerzia:ti,ab,kw OR 'dihydropyridine'/exp OR antihypertensive:ti,ab,kw OR adalat:ti,ab,kw OR afeditab:ti,ab,kw OR nifediac:ti,ab,kw OR nifedipine:ti,ab,kw OR metirosine:ti,ab,kw OR nitroglycerin*:ti,ab,kw OR parzosin:ti,ab,kw OR doxazosin:ti,ab,kw OR phentolamin*:ti,ab,kw OR 'magnesium sulfate':ti,ab,kw	
#2	'premedication'/de OR 'preoperative treatment'/de OR 'preoperative period'/de OR 'perioperative period'/exp OR premedication:ti,ab,kw OR (((preoperative OR 'pre operative' OR perioperative OR 'peri operative' OR presurg* OR 'pre surg*') NEAR/3 (period OR treatment OR management)):ti,ab,kw)	188725
#1	'adrenal tumor'/exp OR 'adrenalectomy'/exp OR 'catecholamine release'/exp OR ('catecholamine'/exp AND 'malignant neoplasm'/exp) OR 'pheochromocytoma'/exp OR phaeochromo*:ti,ab,kw OR pheochromo*:ti,ab,kw OR catecholamine:ti,ab,kw OR ((adrenal NEAR/2 (tumor* OR cancer OR neoplasm OR malignan*)):ti,ab,kw) OR adrenalectom*:ti,ab,kw	139721

Ovid/Medline

#	Searches	Results
15	13 not 12 not 11 OBS	50
14	12 not 11 RCT	31
13	6 and (9 or 10)	80
12	6 and 8	35
11	6 and 7 SR	6
10	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5090509
9	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4076121
8	(exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/)	1353960
7	(meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	548905
6	5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	174
5	limit 4 to yr="2000 -Current"	186
4	1 and 2 and 3	462
3	exp Antihypertensive Agents/ or exp Adrenergic alpha-Antagonists/ or exp Prazosin/ or Phenoxybenzamine/ or Phentolamine/ or Magnesium Sulfate/ or Nitroglycerin/ or alpha-Methyltyrosine/ or exp Calcium Channel Blockers/ or Nifedipine/ or Amlodipine/ or exp Dihydropyridines/ or nifedical.ti,ab,kf. or procardia.ti,ab,kf. or amlor.ti,ab,kf. or katerzia.ti,ab,kf. or antihypertensive.ti,ab,kf. or adalat.ti,ab,kf. or afeditab.ti,ab,kf. or	387409

	nifediac.ti,ab,kf. or nifedipine.ti,ab,kf. or metirosine.ti,ab,kf. or nitroglycerin*.ti,ab,kf. or parzosin.ti,ab,kf. or doxazosin.ti,ab,kf. or phentolamin*.ti,ab,kf. or magnesium sulfate.ti,ab,kf.	
2	Premedication/ or exp Perioperative Period/ or premedication.ti,ab,kf. or ((preoperative or pre operative or perioperative or peri operative or presurg* or pre surg*) adj3 (period or treatment or management)).ti,ab,kf.	151444
1	exp Adrenal Gland Neoplasms/ or Adrenalectomy/ or exp Catecholamines/ or Pheochromocytoma/ or phaeochromo*.ti,ab,kf. or pheochromo*.ti,ab,kf. or catecholamine.ti,ab,kf. or (adrenal adj2 (tumor* or cancer or neoplasm or malignan*)).ti,ab,kf. or adrenalectom*.ti,ab,kf.	330202

Module 7 – Expertisecentrum ACC

Uitgangsvraag
Wat is de plaats van behandeling in een hoog-volume centrum versus behandeling in een laag-volume centrum voor patiënten met een adrenocorticaal carcinoom of een vermoeden daarvan?

Inleiding
Het adrenocorticaal carcinoom (ACC) is een zeldzame en agressieve tumor met een mediane overleving van 3-4 jaar (Fassnacht, 2018). Bij patiënten met een ACC is chirurgische resectie de standaard voor een in opzet curatieve behandeling. Vanwege het zeldzame karakter moet volgens de ESMO-EURACAN-richtlijn moet bijnierchirurgie in het kader van een ACC of een vermoeden daarvan bij voorkeur uitgevoerd worden door chirurgen in centra met voldoende expertise en ervaring (Fassnacht, 2020).
In Nederland bestaat een bijniernetwerk waar de ervaring in zeven ziekenhuizen voor het bijnierschorscarcinoom aanwezig is en die in contact staan om bij individuele casus elkaar te ondersteunen. Echter niet elke patiënt met een ACC of een vermoeden daarop wordt in Nederland standaard geopereerd in een centrum dat is aangesloten bij het Bijniernetwerk. De vraag is daarom of chirurgische behandeling in een expertise centrum of hoog-volume centrum leidt tot betere uitkomsten voor de patiënt.
De nabehandeling van het ACC na curatieve resectie, alsmede de behandeling van gemetastaseerde ziekte valt buiten bespreking in deze richtlijn.

Search and select
A systematic review of the literature was performed to answer the following question:
Is there a benefit of adrenocortical carcinoma (ACC) surgery in a high-volume center when compared to ACC surgery in a low-volume center, for example in regards to overall survival, disease-free survival, progression-free survival, R0 resection, postoperative mortality, complications and length of stay for patients with (suspected) ACC?

P (Patients)	Patients with (suspected) adrenocortical carcinoma (ACC)
I (Intervention)	Surgical treatment for ACC in a high-volume center
C (Control)	Treatment for ACC in a low-volume center
O (Outcomes)	Overall survival, disease-free survival, progression-free survival, R0 resection, postoperative mortality, complications, and length of stay

<u>Relevant outcome measures</u>
The guideline development group considered overall survival, disease-free survival, and progression-free survival as *critical outcome measures* for decision making and R0 resection, postoperative mortality, complications, and length of stay as *important outcome measures* for decision making.

The working group defined the following differences as a minimal clinically (patient) important difference:
Dichotomous outcomes (relative risk, odds ratio):

- Overall survival: Absolute difference >5% or absolute difference >3% and Hazard Ratio (HR) <0.75 (BOM, 2018)
- Disease-free survival: Absolute difference >5%, or absolute difference >3% and HR <0.7 (BOM, 2018)

- Progression-free survival: Absolute difference >5% or absolute difference >3% and Hazard Ratio (HR) <0.7 (BOM, 2018)
- R0 resection: Absolute difference >5% or absolute difference >3% and Hazard Ratio (HR) <0.7
- Postoperative mortality: Absolute difference >5% or absolute difference >3% and Hazard Ratio (HR) <0.7
- Complications: Absolute difference >5% for lethal complications, or >25% for serious complications

Continuous outcomes (mean difference):

- Length of stay: Mean difference > 2 days

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 1-3-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 283 hits. Studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICO;
- The intervention and comparison had to be as defined in the PICO;
- Reported at least one of the outcomes as defined in the PICO;
- Research type: Systematic review, randomized-controlled trial or other comparative (observational) research;
- Articles written in English or Dutch

Sixteen studies were initially selected based on title and abstract screening. After reading the full text, six studies were excluded (see the table with reasons for exclusion under the tab Methods), and ten studies were included.

Results

Ten 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

Anderson (2018) performed a retrospective cohort study using the Healthcare Cost and Utilization Project National Inpatient Sample (NCUP-NIS) dataset. Patients were selected from the HCUP-NIS dataset when they were adult patients and underwent an adrenalectomy between 1998 and 2009 in the United States. A total of 6712 patients were included.

The definition of high- and low volume surgeons was based on the estimated point of annual surgeon volume of adrenalectomies that corresponded to the maximum change in the log odds ratio (OR) of a complication. Restricted Cubic Splines (RCS) was used to examine that point. The identified value was 5.6 (95%CI 3.27-5.96) annual operations. Based on that value, two volume groups were identified. High-volume surgeons had more than six cases per year and low-volume surgeons had six or less cases per year. The high-volume group consisted of 1168 patients and the low-volume group consisted of 5544 patients. Median age in the high-volume group was 56 years (IQR 45-67) and 60 years (IQR 47-70) in the low-volume group. In the high-volume group 395 patients (34%) had a Charleston Morbidity score of two or higher and 2317 patients (42%) in the low-volume group. In the high-volume group 5 patients (5%) and in the low-volume group 2196 patients (40%), were operated in a nonteaching hospital. Groups were not comparable at baseline.

Anderson (2018) used multivariate logistic regression to examine the factors associated with treatment by high-volume surgeon. The primary outcome of this study was incidence of one or more in-hospital complications. Complications were defined by the ICD-9 diagnosis and procedure codes. Secondary outcomes were hospital duration of stay and inflation-adjusted hospital costs.

Barac Nekic (2022) performed a retrospective cohort study using the Croatian ACC registry. Patients were selected from the Croatian ACC registry when they were diagnosed with a European Network for the Study of Adrenal Tumors (ENSAT) stage I-III ACC and receiving surgery between 2008 and 2020. There were no exclusion criteria reported. A center was considered high-volume when the single surgeon who was a urologist, performed more than 20 adrenal surgeries on average per year in the last ten years of which at least two patients per year had ACC.
The high-volume group consisted of 35 patients with a median age of 46 years (IQR 18-77). The low-volume group consisted of 14 patients with a median age of 56.5 years (24-78). Median tumor size in the high-volume group was 80 millimeters (IQR 26-176) and 107.5 millimeters (IQR 70-250) in the low-volume group. Laparoscopic surgery was performed in 71.4 percent in the high-volume group and 28.6 percent in the low-volume group.
Primary outcome of this study was recurrence-free survival (RFS). RFS was calculated from the date of ACC surgery to the date of recurrence or the last imaging follow-up.

Bergamini (2011) performed a prospective cohort study. Patients who were recorded in the Italian Registry of Endoscopic Surgery-Adrenalectomy (IRES-A) between January 2000 and August 2009 and who underwent a laparoscopic adrenalectomy, were included in this study. There were no exclusion criteria reported. The surgical centers were divided in two groups: A referral center with more than 30 laparoscopic adrenalectomies and a non-referral center when there were 30 or less laparoscopic adrenalectomies performed. There was no clear definition of the timeframe in which the number of adrenalectomies had to be performed. The referral center group consisted of 674 patients and the non-referral center consisted of 159 patients. There were no baseline characteristics or prognostic factors reported to provide information on group comparability. The study reported the following outcomes: Complications, intraoperative complications, postoperative surgery-related complications and postoperative nonsurgery-related complications.

Gratian (2014) performed a retrospective cohort study using data from the National Cancer Data Base (NCDB) in the United States between 1998 and 2011. Patients were included with ACC according to the International Classification of Disease for Oncology second and third editions (ICD-O-2/3) for site C74.0-C74.9 and histology 8370.3 (malignant adrenocortical carcinoma) and had no other primary malignancies. Treating facilities were defined as high-volume center when the case load was four or more cases treated per year. A facility was defined as low-volume when the case load was less than four cases treated per year. The high-volume group consisted of 411 patients and the low-volume group consisted of 2354 patients. Median age in the high-volume group was 50 years and in the low-volume group 54 years. Median tumor size in the high-volume group was 11.2 centimeters and in the low-volume group 10.5 centimeters. In the high-volume group, 66 patients (16%) had a Charlson/Deyo comorbidity score of one or more and 603 patients (25.6%) in the low-volume group. The groups were not comparable at baseline. Gratian (2014) reported the outcomes overall survival, 30-day postoperative mortality and length of stay.

Gray (2021) performed a retrospective cohort study using data from the Hospital Episode Statistics (HES) in England. Patients who underwent an unilateral adrenalectomy between

2013 and 2018, were elective readmitted and older than 18 years were included in the study. Data was stratified according to type of procedure, minimally invasive and open procedure. The number of procedures conducted in the year prior to the index procedure was the primary exposure variable. The number of procedures were calculated for each trust (geographically defined catchment area of varying physical size and population) and for each surgeon. Regarding the scope of this review and organization of healthcare in the Netherlands, only outcome data for number of procedures per surgeon, were reported. The threshold according to surgery volume is six, based on the study by Anderson (2018).
In total, 4,189 patients were included in the analysis. 3184 patients (76%) were minimally invasively operated and 1005 patients (24%) were operated using the open procedure. 2622 patients (63%) were operated by a surgeon performing ≥ 6 procedures in the previous year. There are no patient characteristics available for patients operated by a surgeon performing ≥ 6 procedures or < 6 procedures in the previous year.
Gray (2021) reported the outcomes length of stay and complications.

Greco (2011) performed a retrospective cohort study using data from 41 German Urological Centers. Patients who underwent a transperitoneal or retroperitoneal laparoscopic adrenalectomy at the participating centers between 2003 and 2009, were included. The data was stratified according to the surgical approach: Transperitoneal or retroperitoneal. Centers were stratified into three groups according to surgical experience: < 10 laparoscopic adrenalectomies per year (group A), 10-20 laparoscopic adrenalectomies per year (group B) and > 20 laparoscopic adrenalectomies per year (group C). Group A consisted of 73 patients, group B of 91 patients and group C of 199 patients. Mean tumor size for the transperitoneal approach in group A was 2.96 centimeter (SD 1.78), in group B 3.46 centimeter (SD 1.34) and in group C 3.77 centimeter (1.51 SD). Mean tumor size for the retroperitoneal approach was 2.62 centimeter (1.12 SD) in group A, 3.71 centimeter (0.91 SD) in group B and 3.98 centimeter (1.83 SD) in group C. Greco (2011) reported the outcome length of hospital stay.

Hermsen (2012) performed a retrospective cohort study using data from the Dutch Adrenal Network (DAN). Patients older then 16 years, who were treated for histologically confirmed ACC between 1965 and January 2008 in DAN hospitals or non-DAN hospitals with later referral to a DAN hospital, were included. Outcomes were reported for patients treated in a DAN hospital and patients initially treated in a local non-DAN hospital and later directed to a DAN hospital. The DAN hospital group consisted of 89 patients. The non-DAN hospital group consisted of 60 patients. Median age in the DAN group was 48.7 years and in the non-DAN group was 46.1 years. Number of patients with a European Network for the Study of Adrenal Tumors (ENSAT) stage II tumor in the DAN group was 28 (31.5%) and in the non-DAN group 15 (15%). Number of patients with a ENSAT stage III tumor in the DAN group was 34 (38.2%) and in the non-DAN group 17 (28%). Number of patients with a ENSAT stage IV tumor in the DAN group was 25 (28.1%) and in the non-DAN group 27 (45%). Hermsen (2012) reported the outcome overall survival and recurrence-free survival.

Kerkhofs (2013) performed a retrospective cohort study using the data from the Netherlands Cancer Registry. Patients who were diagnosed with ACC between 1st of January 1999 and 31st of December 2008 with primary surgery in a DAN hospital or non-DAN hospital, were included. Pediatric patients were excluded from the analysis. The DAN hospital group consisted of 70 patients and the non-DAN group consisted of 54 patients. Median age in the DAN group was 52 years and in the non-DAN group 57 years. In the DAN group 35 patients (50%) were diagnosed with a ENSAT stage I-II tumor and in the non-DAN group 26 (48%). In the DAN group 11 patients (16%) were diagnosed with ENSAT stage III tumor and 11 patients (20%) in the non-DAN group. Kerkhofs (2013) excluded ENSAT stage IV tumors from the multivariate

analysis because for these patients only palliative treatment in possible. Therefore the influence of the covariate 'surgery' is not expected to be constant in time or comparable between subgroups. Kerkhofs (2013) reported the outcomes median survival, 1-year survival, 5-year survival and overall survival in patients with ENSAT stage I-III ACC.

The studies of **Hermsen (2012)** and **Kerkhofs (2013)** are partially consisting of patients drawn from the same cohort. Both studies report data on overall survival. Kerkhofs (2013) only reports survival data of patients with ENSAT stage I-III ACC. Other outcomes such as 1-year survival, 5-year survival and recurrence-free survival are not reported in both studies. Since the data is not pooled and in consultation with the working group members, data from both studies are reported.

Lombardi (2012) performed a multi-institutional survey in Italy recruiting patients with surgical treatment for ACC between December 2003 and July 2010. Data was compared between two groups: High-volume centers and low-volume centers. A center was considered high-volume if the center recruited 10 or more ACC patients per year. A center was considered low-volume if the recruitment was under 10 ACC patients per year. The high-volume group consisted of 181 patients and the low-volume group consisted of 97 patients. Median age in the high-volume group was 49.2 years and in the low-volume group 50.2 years. Median tumor size in the high-volume group was 104.1 millimeter and 82.8 millimeter in the low-volume group. In total 57 patients (31%) received adjuvant therapy in the high-volume group compared to 13 patients (13%) in the low-volume group. Lombardi (2012) reported the outcomes mean overall survival, which was calculated from the date of diagnosis to the date of death or to the date of the last follow-up, 5-year overall survival rate, mean disease-free survival, which was calculated from the date of diagnosis to the date of diagnosis of tumor recurrence or the date of last follow-up evaluation for patients without recurrence, 5-year disease-free survival rate and R0 resection status. Only univariate analysis for the outcomes were performed.

MacKinney (2022) performed a retrospective cohort study using data from the National Cancer Data Base (NCDB) in the United States. Patients were included when diagnosed with ACC using Primary Site code C74.X and histology codes 8010, 8140 and 8370, between 2004 and 2017. Patients were excluded when treated at more than one reporting facility, receiving palliative surgery, aged under 18 years or treated at a mid-range volume center. Treating facilities were considered high-volume when the center treated fifteen or more ACC cases between 2004 and 2017. Treating facilities were considered low-volume when the center treated seven or less ACC cases between the 2004 and 2017. The high-volume group consisted of 1053 patients and the low-volume group of 1988 patients. Data was stratified according to non-metastatic or metastatic state of the ACC. In the non-metastatic group mean age was 53 years for the high-volume patients and 58 years for the low-volume patients. In the metastatic group mean age was 52 years for the high-volume patients and 58 years for the low-volume patients. MacKinney (2022) reported the outcomes survival, 30-day mortality, 90-day mortality and length of stay.

Table 4: Definitions of high- and low-volume

Study	Definition high-volume	Definition low-volume
Anderson (2018)	≥ 6 adrenalectomies per year per surgeon	< 6 adrenalectomies per year per surgeon
Barac Nekic (2022)	> 20 adrenal surgeries on average per year (2 patients with ACC) by	≤ 20 adrenal surgeries on average per year by a urologist

	single surgeon (urologist) in the last 10 years	or abdominal surgeon in the last 10 years
Bergamini (2011)	> 30 laparoscopic adrenalectomies per center	≤ 30 laparoscopic adrenalectomies per center
Gratian (2014)	≥ 4 patients with adrenal cortical carcinoma treated per year per center	< 4 patients with adrenal cortical carcinoma treated per year per center
Gray (2021)	≥ 6 operations per surgeon in the previous year	< 6 operations per surgeon in the previous year
Greco (2011)	Group A: < 10 laparoscopic adrenalectomies per year per center Group B: 10-20 laparoscopic adrenalectomies per year per center Group C: > 20 laparoscopic adrenalectomies per year per center	
Hermsen (2012)	Dutch Adrenal Network (DAN) hospital	Local hospitals and later direction to DAN hospital
Kerkhofs (2013)	DAN hospital	Non-DAN hospital
Lombardi (2012)	≥ 10 new ACC patients per year per center	< 10 new ACC patients per year per center
MacKinney (2022)	≥ 15 ACC cases per center over 14 years	≤ 7 ACC cases per center over 14 years

Results

Overall Survival

Five studies reported overall survival (OS) (Gratian, 2014; Hermsen, 2012; Kerkhofs, 2013; Lombardi, 2012; MacKinney, 2022).

Gratian (2014) reported median OS of 2.0 years in the high-volume group and 1.9 years in the low-volume group (HR: 0.89 [95%CI 0.70-1.12]). This difference is not clinically relevant.

Hermsen (2012) reported OS of 81 months in the high-volume group and 20 months in the low-volume group. This difference is clinically relevant.

The HR for surgery in a DAN hospital compared with no surgery on overall survival was 1.74 (95%CI 1.34-2.26). The overall survival data is partially overlapping with the overall survival data of Kerkhofs (2013).

Kerkhofs (2013) reported 1-year survival of 93% in the high-volume group and 78% in the low-volume group. The 5-year survival was 63% in the high-volume group and 42% in the low-volume group. This difference is clinically relevant.

The HR for surgery at DAN hospital compared with no surgery on overall survival was 1.96 (95%CI 1.01-3.81). The overall survival data is partially overlapping with the overall survival data of Hermsen (2012).

Lombardi (2012) reported mean OS of 63 months in the high-volume group and 32 months in the low-volume group. The 5-year OS rate in the high-volume group was 52.9% and in the low-volume group 44.4%. This difference is clinically relevant.

MacKinney (2022) reported survival in subgroups for metastatic and non-metastatic ACC. In the metastatic group, survival of the high-volume compared to the low-volume group resulted in a HR 0.74 (95%CI 0.64-0.86), favouring the high-volume group. This difference is clinically relevant. In the non-metastatic group, survival of high-volume compared to low-volume group resulted in HR 0.92 (95%CI 0.81-1.05), favouring the high-volume group.

Because of the heterogeneity of the studies and because some studies did not correct for possible confounders, data was not pooled.

Disease-free survival

Three studies reported disease-free survival (Barac Nekic, 2022; Hermsen, 2012; Lombardi, 2012).

Barac Nekic (2022) reported disease recurrence rate and recurrence free survival. In the high-volume group, eight of thirty-five patients (22.9%) had a recurrence and in the low-volume group eight of fourteen patients (57.1%) had a recurrence. The HR for recurrence-free was 4.55 (95%CI 1.16-17.88), favouring the high-volume group. This difference is clinically relevant.
Hermsen (2012) reported mean recurrence free survival of 69 months in the high-volume group and 22 months in the low-volume group. This difference is clinically relevant.
Lombardi (2012) reported a mean disease-free survival of 24 months in the high-volume group and 15 months in the low-volume group. The 5-year disease-free survival rate was 31.8% in the high-volume group and 26.5% in the low-volume group. This difference was clinically relevant
Because of the small number of studies, heterogeneity of the studies and because some studies did not correct for possible confounders, data was not pooled.

Progression-free survival
No studies reported progression-free survival.

R0 resection status
Two studies reported R0 resection status (Lombardi, 2012; Hermsen, 2012). **Lombardi (2012)** reported R0 resection status in 123 patients (68%) in the high-volume and in 70 patients (72%) in the low-volume group (RR 0.94 [95%CI 0.80-1.10]).
Hermsen (2012) reported R0 resection status in 37 patients (66%) who were operated in a DAN hospital and in 19 patients (34%) who were operated in a non-DAN hospital.
Because of the small number of studies, heterogeneity of the studies and because some studies did not correct for possible confounders, data was not pooled.

Postoperative mortality
Two studies reported postoperative mortality (Gratian, 2014; MacKinney, 2022).
Gratian (2014) reported the 30-day postoperative mortality rate. In the high-volume group the 30-day postoperative mortality rate was 1.9% and in the low-volume group 3.7% (RR 0.59 [95%CI 0.29-1.21]). This difference is not clinically relevant.
MacKinney (2022) reported 30-day and 90-day postoperative mortality for metastatic and non-metastatic ACC. In the metastatic group, the 30-day postoperative mortality rate in the high-volume group was 4.1% and in the low-volume group 4.3%. This difference is not clinically relevant. The 90-day postoperative mortality rate for the metastatic group was 8.3% in the high-volume group and 20.4% in the low-volume group (HR 0.38 [95%CI 0.17-0.84]). This difference is clinically relevant.
In the non-metastatic group, the 30-day postoperative mortality rate for the high-volume group was 2.3% and for the low-volume group 2.4%. This difference is not clinically relevant. The 90-day postoperative mortality rate for the non-metastatic group was 4.7% in the high-volume group and 4.8% in the low-volume group (HR 1.17 [95%CI 0.73-1.90]). This difference is not clinically relevant.
Because of the small number of studies, heterogeneity of the studies and because some studies did not correct for possible confounders, data was not pooled.

Complications
Three studies reported complications (Anderson, 2018; Bergamini, 2011; Gray, 2021).
Anderson (2018) reported any type of complications for 166 patients (14%) in the high-volume group and for 1212 patients (22%) in the low-volume group (OR 0.58 [95%CI 0.43-0.79]). This difference is not clinically relevant.

Bergamini (2011) reported number of complications, intraoperative complications, postoperative surgery and non-surgery related complications. In total, the number of complications was 33 (4.8%) in the high-volume group and 35 (22%) in the low-volume group. This difference is not clinically relevant. Intraoperative complications were reported in fourteen patients (2%) in the high-volume group and for 14 patients (8.2%) in the low-volume group. Postoperative surgery related complications were reported for eight patients (1.2%) in the high-volume group and for four patients (2.5%) in the low-volume group. Postoperative non-surgery related complications were reported for eleven patients (1.6%) in the high-volume group and for eighteen patients (11.3%) in the low-volume group.
Gray (2021) reported adjusted odds ratios for surgeon volume in the 12 months before the index procedure for major post-procedural complications. The complications had to be recorded during index admission or during emergency readmission within 30 days. The reported odds ratios are stratified for minimally invasive and open surgery. The adjusted Odds Ratio (aOR) for complications according to surgeon volume in minimally invasive surgery is 0.99 (95%CI 0.97-1.02) and in open surgery the aOR is 0.96 (95%CI 0.92-1.00). These differences are not clinically relevant.
Because of the small number of studies, heterogeneity of the studies and because some studies did not correct for possible confounders, data was not pooled.

Costs
One study reported costs (Anderson, 2018). **Anderson (2018)** reported inflated-adjusted costs for treatment in high-volume center versus low-volume center. Anderson (2018) reported median cost of $9,884 (IQR 6,955-15,246) in the high-volume group and $11,543 (IQR 7,761-19,397) in the low-volume group (OR -26.2 [95%CI -39.9- to -12.6).

Length of stay
Five studies reported length of stay (Anderson, 2018; Gratian, 2014; Gray, 2021; Greco, 2011; MacKinney, 2022).
Anderson (2018) reported a median duration of stay in the high-volume group of three days (IQR 2-6) and six days (IQR 3-9) in the low-volume group. This difference is clinically relevant.
Gratian (2014) reported median length of stay of five days in the high-volume group and five days in the low-volume group. This difference is not clinically relevant.
Gray (2021) reported adjusted odds ratios for surgeon volume in the 12 months before the index procedure for length of stay greater than the upper quartile. The reported odds ratios are stratified for minimally invasive and open surgery. The adjusted Odds Ratio (aOR) for length of stay according to surgeon volume in minimally invasive surgery is 0.99 (95%CI 0.97-1.01) and in open surgery the aOR is 0.98 (95%CI 0.95-1.01). These differences are not clinically relevant.
Greco (2011) reported mean hospital stay for transperitoneal laparoscopic adrenalectomy (LA) and retroperitoneal LA for three groups stratified according to experience. For the transperitoneal LA, group A (< 10 LA) reported mean hospital stay of 7.83 days (2.99 SD), group B (10-20 LA) reported 7.08 days (2.06 SD) and group C (>20 LA) reported 6.98 days (2.06 SD). The differences are not clinically relevant. Regarding the retroperitoneal LA, group A (<10 LA) reported 7.63 days (1.73 SD), group B (10-20 LA) reported 6.21 days (1.66 SD) and group C (>20 LA) reported 6.82 days (1.75 SD). The differences are not clinically relevant.
MacKinney (2022) reported median length of stay for metastatic and non-metastatic ACC. Median length of stay in the metastatic group was six days for the high-volume group and six days for the low-volume group. Median length of stay in the non-metastatic group was five days for the high-volume group and four days for the low-volume group. Regarding both groups, differences were not clinically relevant.

Because of the heterogeneity of the studies and because some studies did not correct for possible confounders, data could was not pooled.

Level of evidence of the literature

The level of evidence of observational cohort studies is considered low according to the GRADE methodology. Therefore, the level of evidence of these cohort studies starts at low GRADE.

Overall survival

The level of evidence regarding the outcome measure **overall survival** was downgraded by one level because of study limitations (-1; risk of bias regarding adequate follow-up and participant selection). Therefore the evidence was graded as very low.

Disease-free survival

The level of evidence regarding the outcome measure **disease-free survival** was downgraded by two levels because of study limitations (-1; risk of bias regarding assessment of exposure and selection of participants) and number of included patients (-1; imprecision because of low sample size and small number of events per arm). Therefore the evidence was graded as very low.

Progression-free survival

The level of evidence regarding the outcome measure **progression-free survival** could not be assessed with GRADE. None of the studies reported the outcome measure progression-free survival.

R0 resection status

The level of evidence regarding the outcome measure **R0 resection status** was downgraded by one level because of number of included patients (-1; imprecision because of low sample size and small number of events per arm). Therefore the evidence was graded as very low.

Postoperative mortality

The level of evidence regarding the outcome measure **postoperative mortality** was downgraded by two levels because of study limitations (-1; risk of bias regarding reporting of follow-up) and number of included patients (-1; imprecision because of low sample size and small number of events per arm). Therefore the evidence was graded as very low.

Complications

The level of evidence regarding the outcome measure **complications** was downgraded by two levels because of study limitations (-1; risk of bias regarding confounding, reporting of follow-up and unknown co-interventions) and number of included patients (-1; imprecision because of low sample size and small number of events per arm). Therefore the evidence was graded at very low.

Costs

The level of evidence regarding the outcome measure **costs** was downgraded by two levels because of study limitations (-1; risk of bias regarding follow-up and unkown co-interventions) and number of included patients (-1; imprecision because of low sample size). Therefore the evidence was graded at very low.

Length of stay
The level of evidence regarding the outcome measure **length of stay** was downgraded by two levels because of study limitations (-2; risk of bias regarding selection of participants, confounding, adequate follow-up and unknown co-interventions). Therefore the evidence was graded at very low.

Conclusions
Overall survival

Very low GRADE	The evidence is very uncertain about the effect of treatment in a high-volume center on overall survival when compared with treatment in a low-volume center in patients with ACC. *Source: Gratian, 2014; Hermsen, 2012; Kerkhofs, 2013; Lombardi, 2012; MacKinne, 2022*

Disease-free survival

Very low GRADE	The evidence is very uncertain about the effect of treatment in a high-volume center on disease-free survival when compared with treatment in a low-volume center in patients with ACC. *Source: Barac Nekic, 2022; Hermsen 2012; Lombardi, 2012*

Progression-free survival

No GRADE	No evidence was found regarding the effect of treatment in a high-volume center on progression-free survival when compared with treatment in a low-volume center in patients with ACC.

R0 resection status

Very low GRADE	The evidence is very uncertain about the effect of treatment in a high-volume center on R0 resection status when compared with treatment in a low-volume center in patients with ACC. *Source: Lombardi, 2012; Hermsen, 2012*

Postoperative mortality

Very low GRADE	The evidence is very uncertain about the effect of treatment in a high-volume center on postoperative mortality when compared with treatment in a low-volume center in patients with ACC. *Source: Gratian, 2014; MacKinney, 2022*

Complications

Very low GRADE	The evidence is very uncertain about the effect of treatment in a high-volume center on complications when compared with treatment in a low-volume center in patients with ACC. *Source: Anderson, 2018; Bergamini, 2011; Gray, 2021*

Costs

Very low GRADE	The evidence is very uncertain about the effect of treatment in a high-volume center on costs when compared with treatment in a low-volume center in patients with ACC. *Source: Anderson, 2018*

Length of stay

Very low GRADE	The evidence is very uncertain about the effect of treatment in a high-volume center on length of stay when compared with treatment in a low-volume center in patients with ACC. *Source: Anderson, 2018; Gratian, 2014; Gray, 2021; Greco, 2011; MacKinney, 2022*

Overwegingen – van bewijs naar aanbeveling

Bijnierschorscarcinoom is een zeer zeldzame ziekte, waarbij de incidentie ligt rond de 1 per 1 miljoen (Kerkhofs, 2013). Gecontroleerde studies bij een dergelijke incidentie zijn praktisch onhaalbaar. De systematische search naar de verschillen tussen hoog- en laagvolume centra in de behandeling, operatief, van bijnierschorscarcinoom resulteerde in negen observationele cohort studies (Anderson, 2018; Barac Nekic, 2022; Bergamini, 2011; Gratian, 2014; Gray, 2021; Greco, 2011; Hermsen, 2012; Kerkhofs, 2013; Lombardi, 2012, MacKinney, 2022).

In deze literatuur werd geen eenduidige definitie gevonden van hoog- en laagvolume centrum. Met de beschreven incidentie van 1 per 1 miljoen is een 'hoog' volume centrum nog steeds laag vergeleken met sommige andere tumorsoorten. In de artikelen die specifiek bijnierschorscarcinoom met een getal benoemden was het criterium voor hoog-volume centrum vanaf één per jaar per centrum tot zes per jaar per chirurg, waarbij ook andere bijnieroperaties werden opgenomen met wisselende getallen. Enkele artikelen beschreven als criterium het aantal patiënten behandeld in het centrum, dus in het team voor de ziekte.

Voor twee van de drie cruciale uitkomstmaten (totale overleving en ziektevrije overleving) werden resultaten gerapporteerd (zie tabel 2).

Tabel 2. Resultaten cruciale uitkomstmaten totale overleving en ziektevrije overleving

Uitkomstmaat	Studie	Hoog-volume versus laag-volume	Sterkte van bewijs	Opmerkingen
Totale overleving	Gratian (2014)	Voordeel voor hoog-volume centrum, geen klinisch relevant verschil	Zeer laag	Overlevingsdata voor patiënten in alle tumor stadia
	Hermsen (2012)	Voordeel voor Dutch Adrenal Network (DAN) centrum, gevonden verschil is klinisch relevant		Data van Hermsen (2012) en Kerkhofs (2013) overlappen gedeeltelijk. Alleen overlevingsdata voor patiënten met ENSAT tumor stadium I-III
	Kerkhofs (2013)	Voordeel voor DAN centrum, gevonden verschil is klinisch relevant		
	Lombardi (2012)	Voordeel voor hoog-volume centrum, verschil is klinisch relevant		Overlevingsdata voor patiënten in alle tumor stadia
	MacKinney (2022)	Voordeel voor hoog-volume centrum gevonden, verschil is klinisch relevant		Overlevingsdata voor patiënten in alle tumor stadia

Ziektevrije overleving	Barac Nekic (2022)	Voordeel voor hoog-volume centrum, gevonden verschil is klinisch relevant	Zeer laag	
	Hermsen (2012)	Voordeel voor Dutch Adrenal Network (DAN) centrum, gevonden verschil is klinisch relevant		
	Lombardi (2012)	Voordeel voor hoog-volume centrum, gevonden verschil is klinisch relevant.		

Voor de vier belangrijke uitkomstmaten (R0 resectie status, postoperatieve mortaliteit, complicaties en opnameduur) werden resultaten gerapporteerd. Gezien het risico op bias, de inconsistentie, toepasbaarheid en kleine aantallen in sommige studies, is het voor deze uitkomstmaten lastig om hier conclusies aan te verbinden.

Eén studie rapporteerde R0 resectie status waarbij er een geen klinisch relevant verschil tussen de behandelgroepen gevonden was. Twee studies rapporteerden postoperatieve mortaliteit waarbij er één studie 90 dagen postoperatieve mortaliteit rapporteerde en een klinisch relevant verschil vond in het voordeel van hoog-volume centra voor patiënten met metastasen. De 90 dagen postoperatieve mortaliteit voor patiënten zonder metastasen en 30 dagen postoperatieve mortaliteit, lieten geen klinisch relevant verschil zien tussen hoog- en laag-volume centra. Drie studies rapporteerden complicaties waarbij beide studies geen klinisch relevant verschil vonden tussen de behandelgroepen. Vijf studies rapporteerden opnameduur, waarvan twee studies alleen over bijnierschorscarcinoom en drie over alle bijnieroperaties gingen. Er werden geen klinisch relevante verschillen zijn gevonden bij deze uitkomst.

De bewijskracht voor alle uitkomstmaten gezamenlijk is zeer laag. Observationele studies starten, volgens de GRADE methodiek, op een laag bewijskracht niveau (Schünemann, 2013). Er is daarnaast afgewaardeerd vanwege risico op bias omdat de follow-up periode in sommige gevallen niet beschreven was, mogelijke confounders niet in de analyse zijn meegenomen of er bij een aantal studies de co-interventies en mogelijk verschil tussen de behandelgroepen, niet beschreven zijn. Er kan daarom op basis van de gevonden literatuur geen eenduidige conclusie getrokken worden met betrekking tot het effect van hoog- en laag-volume centra op overleving, resectie status, postoperatieve mortaliteit, kosten of opnameduur.

Naast de beschikbare wetenschappelijke literatuur zijn er ook een aantal overwegingen die meespelen met betrekking tot de keuze voor een behandeling in een hoog-volume centrum of een laagvolume centrum voor patiënten met het zeldzame bijnierschorscarcinoom.
Meestal is het voorafgaand aan de operatie onzeker of de tumor anatomisch gelokaliseerd bij de bijnier, een bijnierschorscarcinoom betreft. In de afweging bij een operatie met vooraf een onzekere diagnose (benigne of maligne bijniertumor) moet vanwege de kans op een bijnierschorscarcinoom de operatie in een voor bijnierschorscarcinoom gespecialiseerd centrum worden verricht, onafhankelijk van de eventuele bewijslast. Het gaat dan niet alleen om de chirurg, maar om het hele team, inclusief endocrinoloog, oncoloog et cetera, met daarbij de organisatie en infrastructuur voor diagnostiek, nabehandeling, (psychosociale) nazorg en palliatieve zorg. Daarnaast moet iedere patiënt, conform SONCOS normeringsrapport, een vast aanspreekpunt c.q. casemanger krijgen.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Patiëntvoorkeur speelt een belangrijke rol in de keuze van de ingreep. Goede informatie over de behandelopties aan de patiënt in een open communicatie is essentieel. In het algemeen, vanuit medische kant, wordt verwijzing naar een bijnier expertise centrum geadviseerd. Het kan zijn dat de patiënt een voorkeur heeft voor een bepaald centrum of kiest voor behandeling dichterbij huis waarbij het gekozen centrum wellicht geen expertise centrum is.

Kosten (middelenbeslag)
Eén studie rapporteerden kosten (Anderson, 2018) waarbij de kosten voor behandeling in een hoog-volume centrum 9,884 dollar zijn (IQR 6,955-15,246) en de kosten voor behandeling in een laag-volume centrum 11,543 dollar zijn (IQR 7,761-19,397). De kosten zijn aangepast aan de inflatie maar volgens het Amerikaanse systeem berekend.
Het is niet mogelijk om deze kosten te generaliseren naar de Nederlandse situatie. Een valide schatting van de kosten voor een operatie en nazorg voor mensen met bijnierschorscarcinoom is op basis van de search niet te maken. De werkelijke kosten per ziekenhuis zullen verschillen, mede afhankelijk van de gemaakte afspraken met de zorgverzekeraar. Op basis van de kosten kan geen aanbeveling worden gedaan ten aanzien van behandelen van patiënten in een hoog- of laagvolume centrum.

Aanvaardbaarheid, haalbaarheid en implementatie
Vanwege de zeldzaamheid van de ziekte bijnierschorscarcinoom zal zowel de mens met de (verdenking) op deze ziekte, als een arts die de diagnose bijnierschorscarcinoom of een verdenking daarop stelt, het beste voor hebben en willen kiezen voor behandeling door een ervaren arts, werkende in een relevant multidisciplinair team.
De algemene normen voor bijnieroperaties, in Nederland gesteld door SONCOS op twintig operaties per jaar per centrum (Platform oncologie - SONCOS, 2023), kunnen niet zonder meer één op één vertaald worden voor operaties voor (verdenking op) bijnierschorscarcinoom. De Soncos-normen van twintig bijnieroperaties per jaar zijn niet met bewijs onderbouwd maar op consensus binnen de chirurgische beroepsgroep gebaseerd. De huidige search geeft hiervoor ook geen bewijs.

De risico's voor de toekomst om mensen met een bijnierschorscarcinoom niet te laten behandelen in een team van voor deze ziekte ervaren specialisten, ligt in onbekendheid van de arts die een dergelijke bijniertumor ontdekt en zijn of haar verwachting dat een snelle en eenvoudige operatie kan volstaan.

Aanbeveling:
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
De bewijslast is te laag om een goed onderbouwde conclusie te geven over het verschil tussen hoog- en laagvolume centra voor de operatie en behandeling van bijnierschorscarcinoom gerelateerd op overleving, mortaliteit, complicaties etc.

Het gebrek aan bewijskracht om specifieke vragen over zeldzame ziekten te beantwoorden is niet onverwacht. De uitkomsten uit de literatuur laten de trend zien dat behandeling van mensen met een bijnierschorscarcinoom in een hoog-volume centrum beter kan zijn dan daarbuiten. Gecombineerd met expert opinion en de geanticipeerde wens van de patiënt om behandeld te worden door een specialist die ervaring heeft met het ziektebeeld, komen wij tot onderstaande aanbeveling.

Behandel bij voorkeur patiënten met (verdenking op) een adrenocorticaal carcinoom in een centrum gespecialiseerd in deze ziekte.

Een centrum specificeert zich door te fungeren als (tertiair) verwijscentrum voor deze ziekte met een team van ervaren specialisten in de diagnostiek, therapie en follow up.

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Bijlagen bij module Expertisecentrum ACC

Evidence tables

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies)

Research question: What is the effect of adrenocortical carcinoma (ACC) surgery performed in a high-volume or expert center when compared to ACC surgery in a different center on overall survival, disease-free survival, progression-free survival, R0 resection, postoperative mortality, complications and length of stay for patients with (suspected) ACC?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Anderson, 2018	Type of study: Retrospective cohort study Database and country: Hospital setting, HCUP-NIS database, USA Funding and conflicts of interest: Not reported	Inclusion criteria: - Adult patients who underwent adrenalectomy from 1998-2009 in the US Exclusion criteria: - Patients from Arizona, Colorado, Kentucky, Michigan, Missouri, New Jersey, Oregon, Tennessee and Washington N total at baseline: Intervention: 1168 Control: 5544 Important prognostic factors[2]: *Median Age in years (IQR):* *I: 56 (45-67)*	Describe intervention: Patients treated by surgeons who performed ≥ 6 adrenalectomy cases per year	Describe control: Patients treated by surgeons who performed < 6 adrenalectomy cases per year.	Length of follow-up: Not reported Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Any complication I: N=166 (14%) C: N=1212 (22%) OR (95%CI) : 0.58 (0.43-0.79) Inflated-adjusted costs, median (IQR): I: $ 9884 (6955-15246) C: $ 11543 (7761-19397) OR (95%CI): -26.2 (-39.9—12.6) Duration of stay, median days (IQR): I: 3 (2-6)	*Authors conclusion:* This study illustrates that patients who undergo adrenalectomy by a high-volume surgeon (≥6 cases/year) were less likely, on average, to experience a complication, have a prolonged hospital duration of stay, and incur greater costs for their treatment compared with if they had the procedure by a low-volume surgeon whose median case volume was just one case annually. This study performed an Restricted Cubic Splines method and bootstrap simulation to estimate the point of annual surgeon volume that corresponds to

		C: 60 (47-70) *Race, white n:* *I: 913 (78%)* *C: 3866 (70%)* *Race, black n:* *I: 80 (7%)* *C: 629 (11%)* *Race, Hispanic n:* *I: 56 (5%)* *C: 431 (8%)* *Race, other n:* *I: 56 (5%)* *C: 261 (5%)* *Gender, Female n:* *I: 602 (52%)* *C: 2779 (50%)* *Charleston Comorbidity score ≥2, n:* *I: 395 (34%)* *C: 2317 (42%)* *Primary insurance, Private n:* *I: 698 (60%)* *C: 2525 (46%)* *Hospital type, nonteaching, n:* *I: 45 (5%)* *C: 2196 (40%)* Groups not comparable at baseline				C: 6 (3-9) RR (95%CI): 0.69 (0.59-0.80)	the maximum change in log OR of a complication. After establishing the volume groups high (≥6) versus low (<6), multivariate logistic regression was also used to examine the adjusted association between low- versus high-volume surgeons and the incidence of any postoperative complication. A priori covariates were identified to adjust for in the regression analysis. There was no clear definition of length of follow-up in which complications could appear.

Barac Nekic, 2022	Type of study: Retrospective cohort study Database and country: Croatian ACC Registry, Croatia Funding and conflicts of interest: Research received no external funding and authors declared no conflict of interest	Inclusion criteria: - Patients with European Network for the Study of Adrenal Tumors (ENSAT) stage I-III ACC - Patients who received adrenal surgery between 2008 and 2020. Exclusion criteria: No exclusion criteria reported N total at baseline: Intervention: 35 Control: 14 Important prognostic factors[2]: *Median Age in years (IQR):* *I: 46 (18-77)* *C: 56.5 (24-78)* *Gender, Female, n:* *I: 24 (69%)* *C: 10 (71%)* *Median tumor size in mm (IQR):* *I: 80 (26-176)* *C: 107.5 (70-250)* *ENSAT tumor stage I, n:* *I: 6 (17%)* *C: 0 (0%)* *ENSAT tumor stage II, n:* *I: 21 (60%)* *C: 10 (71%)* *ENSAT tumor stage III, n:*	Describe intervention: Adrenal surgery by a single surgeon who was a urologist in a high-volume center. Centers were considered high-volume if they had an average of > 20 adrenal surgeries per year per surgeon in the last 10 years, of which at least two patients per year had ACC.	Describe control: Adrenal surgery by a urologist or abdominal surgeon in a low-volume center.	Length of follow-up: Median length of follow-up in months (IQR): I: 62 (5-147) C: 61.5 (5-165) Loss-to-follow-up: I: N=0 (0%) C: N=0 (0%) Incomplete outcome data: I: N=0 (0%) C: N=0 (0%)	Outcome measures and effect size (include 95%CI and p-value if available): Disease recurrence I: N=8 (22.9%) C: N=8 (57.1%) Recurrence-free survival HR 4.55 (95%CI 1.16-17.88)	*Authors conclusion:* The results of this study showed that ACC surgery performed in expert centers was associated with a better oncological outcome in terms of lower risk of disease recurrence and a tendency towards improved survival rate. Groups are not comparable at baseline. Patients in the low-volume group had larger tumors (tumor size) and there were less laparoscopic adrenalectomies performed in the low-volume group. There was no clear definition of low-volume surgeries.

		I: 8 (23%) *C: 4 (29%)* *Laparoscopic surgery, n:* *I: 25 (71.4%)* *C: 4 (28.6%)* Groups not comparable at baseline					
Bergamini, 2011	Type of study: Prospective cohort study Database and country: Italian Registry of Endoscopic Surgery-Adrenalectomy (IRES-A), Italy Funding and conflicts of interest: Researchers reported no conflict of interest to be disclosed and no financial support to be obtained.	Inclusion criteria: - Patients who were recorded in the IRES-A database from January 2000 until august 2009 - Patients who underwent laparoscopic adrenalectomy - Completion of informed consent Exclusion criteria: No exclusion criteria reported N total at baseline: Intervention: 674 Control: 159 Important prognostic factors[2]: *Gender, Female:* *Total, n: 521 (63%)* No information on group comparability.	Describe intervention: Laparoscopic adrenalectomy in a referral center with > 30 adrenalectomies.	Describe control: Laparoscopic adrenalectomy in a non-referral center with ≤ 30 adrenalectomies.	Length of follow-up: Not reported Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Number of complications: I: N=33 (4.8%) C: N=35 (22%) Intraoperative complications: I: N=14 (2%) C: N=13 (8.2%) Postoperative surgery-related complications: I: N=8 (1.2%) C: N=4 (2.5%) Postoperative nonsurgery-related complications: I: N=11 (1.6%) C: N=18 (11.3%)	*Authors conclusion:* The opinion of these authors is that the inexperience of a surgeon may be a relevant factor in the occurrence of these adverse events. The main risk factors, for the occurrence of complications during laparoscopic adrenalectomy appear to be surgical inexperience, the age and BMI of the patient, the dimension of the mass, and pheochromocytoma. There are no baseline characteristics for the subgroups referral and non-referral center. There was no exact definition of the timeframe in which the number of adrenalectomies had to be performed to be a referral or non-referral center.
Gratian, 2014	Type of study: Retrospective cohort study	Inclusion criteria: - Patients with ACC (ICD-O-2/3 for site C74.0-C74.9 and histology 8370.3) who were recorded from	Describe intervention: Treatment at a high-volume center with an annual case load of ≥ 4 cases of primary adrenal	Describe control: Treatment at a low-volume center with an annual case load of < 4 cases of primary adrenal	Length of follow-up: At least 5-years for outcome Overall Survival	Outcome measures and effect size (include 95%CI and p-value if available):	*Authors conclusion:* This study did not find an association between hospital case volume and OS despite more aggressive surgical and

	Database and country: National Cancer Data Base, United States Funding and conflicts of interest: Not reported	the National Cancer Data Base (NCDB) between 1998 and 2011 - Patients had no other primary malignancies Exclusion criteria: No exclusion criteria reported N total at baseline: Intervention: 411 Control: 2354 Important prognostic factors[2]: *Median Age in years (Q1, Q3):* *I: 50 (41, 60)* *C: 54 (43, 65)* *Gender, Female, n:* *I: 236 (57.4%)* *C: 1410 (59.9%)* *Median tumor size in cm (Q1, Q3):* *I: 11.2 (8.0, 16.0)* *C: 10.5 (7.1, 15.0)* *Charlson/Deyo score ≥1, n:* *I: 66 (16%)* *C: 603 (25.6%)* Groups were not comparable at baseline.	malignancies treated per year.	malignancies treated per year.	Loss-to-follow-up: Not reported Incomplete outcome data: Missing data are <5% except for: Charlson/Deyo score: 30% Income: 6% Distant metastasis: 84% Tumor grade: 77% Clinical stage:84%	Median Overall survival: I: 2.0 years C: 1.9 years HR (95%CI): 0.89 (0.70-1.12) 30-day postoperative mortality I: 1.9% C: 3.7% Median Length of stay: I: 5 days C: 5 days	adjuvant therapy at high-volume centers. Groups were not comparable at baseline. In the high-volume group median tumor size was larger. In the low-volume group median age was higher and patients had more comorbidities (Charlson/Deyo score).
Greco, 2011	Type of study: Prospective cohort study	Inclusion criteria: - Patients who underwent a transperitoneal or retroperitoneal laparoscopic	Describe intervention: Centres were stratified into three groups according to experience:	Describe control: Not applicable	Length of follow-up: No follow-up reported Loss-to-follow-up:	Outcome measures and effect size (include 95%CI and p-value if available):	*Authors conclusion:* According to the present study, LA for malignant adrenal tumors should be performed only in high-

	Database and country: 23 German Urological centers, Germany Funding and conflicts of interest: No declaration of conflict of interest	adrenalectomy (LA) at participating centres between 2003 and 2009 <u>Exclusion criteria</u>: Not reported <u>N total at baseline</u>: Group A: 73 Group B: 91 Group C: 199 <u>Important prognostic factors</u>[2]: *Transperitoneal LA:* *Mean Age in years (SD):* *Group A: 56.12 (1.98)* *Group B: 62.24 (12.28)* *Group C: 54.66 (12.65)* *Retroperitoneal LA:* *Mean Age in Years (SD):* *Group A: 54.12 (13.32)* *Group B: 41.71 (13.25)* *Group C: 56.37 (16.14)* *Transperitoneal LA* *Mean tumor size in cm (SD):* *Group A: 2.96 (1.78)* *Group B: 3.46 (1.34)* *Group C: 3.77 (1.51)* *Retroperitoneal LA* *Mean tumor size in cm (SD):* *Group A: 2.62 (1.12)* *Group B: 3.71 (0.91)* *Group C: 3.98 (1.83)* Groups were not comparable at baseline.	- Group A: < 10 laparoscopic adrenalectomies per year - Group B: 10-20 laparoscopic adrenalectomies per year - Group C: > 20 laparoscopic adrenalectomies per year Data was also stratified according to the surgical approach (transperitoneal or retroperitoneal)		Not reported <u>Incomplete outcome data</u>: Not reported	Mean Hospital stay (SD): *Transperitoneal LA* Group A: 7.83 days (2.99) Group B: 7.08 days (2.06) Group C: 6.98 days (2.06) *Retroperitoneal LA* Group A: 7.63 days (1.73) Group B: 6.21 days (1.66) Group C: 6.82 days (1.75)	volume centers by a surgeon performing >10 LAs/year. Correlation between tumour size and operating time and duration of stay. No follow-up or missing data reported. Only urological departments

Hermsen, 2012	Type of study: Retrospective cohort study Database and country: Dutch Adrenal Network, the Netherlands Funding and conflicts of interest: Not reported	Inclusion criteria: - Patients who were operated from 1965 until January 2008 in DAN hospitals and patients who were operated in non-DAN hospitals and later directed to a DAN hospital - Age > 16 years - Histologically confirmed ACC - Patients with stage IV ACC who were not operated Exclusion criteria: - Not reported N total at baseline: Intervention: 89 Control: 60 Important prognostic factors[2]: *Median Age in years (range):* *I: 48.7 (21-79)* *C: 46.1 (16-71)* *Tumor ENSAT stage I at diagnosis:* *I: N=2 (2.2%)* *C: N=1 (2%)* *Tumor ENSAT stage II at diagnosis:* *I: N=28 (31.5%)* *C: N=15 (15%)*	Describe intervention: Surgery or treatment for ACC at a Dutch Adrenal Network (DAN) hospital	Describe control: Surgery or treatment for ACC in a local hospital and later directed to a DAN hospital.	Length of follow-up: Median follow-up (range): 25 months (0-451) Loss-to-follow-up: Not reported Incomplete outcome data: Resection status: N=14 (14%)	Outcome measures and effect size (include 95%CI and p-value if available): Overall survival (local hospital versus DAN hospital): I: 81 months C: 20 months Multivariate analysis of Surgery at DAN hospital on overall surviva: HR (95%CI): 1.74 (1.34-2.26) Recurrence-free survival: I: 69 months (range 36-102) C: 22 months (range 0-50)	*Authors conclusion:* Treatment in specialized centers offering multidisciplinary approach is beneficial to patients with ACC, because improved survival was observed in patients initially operated within DAN hospitals compared with patients treated in non-DAN hospitals. The database only contains patients who have been treated in a DAN center at any time during course of their disease. Patients with ENSAT tumor stage IV who did not undergo an operation were also included

		Tumor ENSAT stage III at diagnosis: *I: N=34 (38.2%)* *C: N=17 (28%)* *Tumor ENSAT stage IV at diagnosis:* *I: N=25 (28.1%)* *C: N=27 (45%)* Groups were not comparable at baseline.					
Kerkhofs, 2013	Type of study: Retrospective cohort study Database and country: Netherlands Cancer Registry, the Netherlands Funding and conflicts of interest: The authors declare no conflict of interest. This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector	Inclusion criteria: - Adults who were diagnosed with ACC between 1st January 1999 and 31st December 2008 - Primary surgery in a Dutch Adrenal Network (DAN) hospital or non-DAN hospital Exclusion criteria: - Pediatric patients N total at baseline: Intervention: 70 Control: 54 Important prognostic factors[2]: *Median Age in years (range):* *I: 52 (22-74)* *C: 57 (28-80)* *Gender, Female, n:* *I: 44 (63%)* *C: 29 (54%)* *Tumor ENSAT stage I-II:* *I: N=35 (50%)*	Describe intervention: Primary surgery in a DAN hospital	Describe control: Primary surgery in a non-DAN hospital	Length of follow-up: At least 1 year Loss-to-follow-up: Surgery unspecified: N=15 Incomplete outcome data: I: N=24 (34%) C: N=17 (32%) Reasons: Stage IV ACC was left out of the Cox model because clinically these patients belong to a different category. Only palliative treatment is possible for these patients, therefore the influence of the covariate 'surgery' is not expected to be constant in time or comparable in subgroups.	Outcome measures and effect size (include 95%CI and p-value if available): Median survival (95%CI): I: Not reported C: 49 months (24-75) 1-year survival: I: 93% C: 78% 5-year survival: I: 63% C: 42% Overall survival (non-DAN hospital versus DAN hospital): HR (95%CI): 1.96 (1.01-3.81)	*Authors conclusion:* The results of our population-based study confirm that surgical removal of the primary tumor in a DAN hospital is associated with a survival benefit compared with primary surgery in a non-DAN hospital for patients with local or locally advanced ACC. Only survival data for ENSAT stage I-III ACC. The study included surgical and non-surgical patients

		C: N=26 (48%) *Tumor ENSAT stage III:* *I: N=11 (16%)* *C: N=11 (20%)* *Tumor ENSAT stage IV:* *I: N=23 (33%)* *C: N=9 (17%)* Groups were not comparable at baseline.					
Lombardi, 2012	Type of study: Multi-institutional survey Database and country: Multi-institutional survey data, Italy Funding and conflicts of interest: No conflict of interest. Funding not reported.	Inclusion criteria: - Patients with surgical treatment for ACC between December 2003 and July 2010 Exclusion criteria: Not reported N total at baseline: Intervention: 181 Control: 97 Important prognostic factors[2]: *Median Age in years (range):* *I: 49.2 (10-81)* *C: 50.2 (10-81)* *Gender, Female, n:* *I: 109 (60%)* *C: 56 (57%)* *Median tumor size in mm (range):* *I: 104.1 (30-340)* *C: 82.8 (30-200)*	Describe intervention: Treatment in a high-volume center with an annual case load of ≥ 10 ACC patients per center	Describe control: Treatment in a low-volume center with an annual case load of < 10 ACC patients per center	Length of follow-up: Mean follow-up time (SD): I: 36.5 months (38.7) C: 30.5 months (30.4) Loss-to-follow-up: I: N=33 (18%) C: N=16 (16%) Reasons (describe): Not reported Incomplete outcome data: Number of missing cases with follow-up data is reported at loss-to-follow-up.	Outcome measures and effect size (include 95%CI and p-value if available): Mean overall survival: I: 63 months C: 32 months 5-year overall survival rate: I: 52.9% C: 44.4% Mean disease-free survival: I: 24 months C: 15 months 5-year disease-free survival rate: I: 31.8% C: 26.5% Resection status R0: I: N=123 (68%) C: N=70 (72%)	*Authors conclusion:* Patients that underwent surgery at HVC experienced a better oncologic outcome, with a significantly longer time to recurrence and a lower rate of local recurrence observed. Only univariate analysis for outcomes Rate of patients with adjuvant therapy and laparoscopic resection were significantly higher in HVC group compared to LVC group.

		Tumor ENSAT stage I: *I: N=22 (12%)* *C: N=11 (11%)* *Tumor ENSAT stage II:* *I: N=80 (44%)* *C: N=43 (44%)* *Tumor ENSAT stage III:* *I: N=43 (24%)* *C: N=23 (24%)* *Tumor ENSAT stage IV:* *I: N=27 (15%)* *C: N=14 (14%)* *Adjuvant therapy, mitotane:* *I: N=23 (13%)* *C: N=3 (3%)* *Adjuvant therapy, polychemotherapy (PCT):* *I: N=10 (6%)* *C: N=9 (9%)* *Adjuvant therapy, mitotane + PCT:* *I: N=24 (13%)* *C: N=1 (1%)* Groups were not comparable at baseline.					
MacKinney, 2022	Type of study: Retrospective cohort study Database and country: National Cancer Data Base, United States	Inclusion criteria: - Patients in the National Cancer Data Base diagnosed with ACC using Primary Site code C74.X and histology codes 8010, 8140 or 8370 between 2004 and 2017	Describe intervention: Patients treated in a high-volume center with ≥15 ACC cases from the 2004-2017 time period	Describe control: Patients treated in a low-volume center with ≤7 ACC cases from the 2004-2017 time period	Length of follow-up: Not reported Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): Survival – non metastatic group: HR (95%CI): 0.92 (0.81-1.05)	*Authors conclusion:* NM-ACC having surgery at HVCs and LVCs had similar OS. M-ACC at HVCs had improved OS and 90-day mortality. It may be more important with regards to outcomes for a patient with M-ACC to be

	Funding and conflicts of interest: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. Authors have no related conflicts of interest to declare.	Exclusion criteria: - Patients treated at more than one reporting facility - Patients receiving palliative surgery - Age < 18 years - Patients from centers with a mid-range volume N total at baseline: Intervention: 1053 Control: 1988 Important prognostic factors[2]: ***Non-metastatic group:*** *Mean Age in years (SD):* *I: 53 (15)* *C: 58 (16)* *Gender, Female, n:* *I: 416 (57.4%)* *C: 748 (60.9%)* *Charlson Comorbidity Index, 0:* *I: N=569 (78.5%)* *C: N=843 (68.6%)* *Charlson Comorbidity Index, 1:* *I: N=111 (15.3%)* *C: N=276 (22.5%)* *Charlson Comorbidity Index, ≥2:* *I: N=45 (6.2%)* *C: N=110 (9%)* *Tumor size <5.0 cm:* *I: N=81 (11.2%)* *C: N=173 (14.1%)*				Survival – metastatic group: HR: (95%CI): 0.74 (0.64-0.86) 30-day mortality – non metastatic group: I: N=14 (2.3%) C: N=22 (2.4%) 30-day mortality – metastatic group: I: N= 5 (4.1%) C: N=6 (4.3%) 90-day mortality – non metastatic group: I: N=29 (4.7%) C: N=42 (4.8%) HR (95%CI): 1.17 (0.73-1.90) 90-day mortality – metastatic group: I: N=10 (8.3%) C: N=28 (20.4%) HR (95%CI): 0.38 (0.17-0.84) Median Length of stay (Q1-Q3) – non metastatic group: I: 5 days (3-7) C: 4 days (2-7) Median Length of stay (Q1-Q3) – metastatic group: I: 6 days (4-9) C: 6 days (3-8)	treated at a HVC than a patient with NM-ACC. No length of follow-up or missing data reported. Patients in HVC were more likely to get surgery than patients in LVC.

		Tumor size 5.0-9.9 cm: *I: N=241 (33.2%)* *C: N=436 (35.5%)* *Tumor size ≥10.0 cm:* *I: N=350 (48.3%)* *C: N=503 (40.9%)* ***Metastatic group:*** *Mean Age in years (SD):* *I: 52 (16)* *C: 58 (15)* *Gender, Female, n:* *I: 193 (58.8%)* *C: 391 (56.7%)* *Charlson Comorbidity Index, 0:* *I: N=238 (72.6%)* *C: N=483 (70.1%)* *Charlson Comorbidity Index, 1:* *I: N=61 (18.6%)* *C: N=131 (19.0%)* *Charlson Comorbidity Index, ≥2:* *I: N=29 (8.8%)* *C: N=29 (4.2%)* *Tumor size <5.0 cm:* *I: N=25 (7.6%)* *C: N=62 (9.0%)* *Tumor size 5.0-9.9 cm:* *I: N=67 (20.4%)* *C: N=185 (26.9%)* *Tumor size ≥10.0 cm:*					

		I: N=175 (53.4%) *C: N=296 (43%)* Groups were not comparable at baseline.					

Notes:

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

Risk of bias table for cohort studies

Research question: What is the effect of adrenocortical carcinoma (ACC) surgery performed in a high-volume or expert center when compared to ACC surgery in a different center on overall survival, disease-free survival, progression-free survival, R0 resection, postoperative mortality, complications and length of stay for patients with (suspected) ACC?

Author, year	Selection of participants Was selection of exposed and non-exposed cohorts drawn from the same population?	Exposure Can we be confident in the assessment of exposure?	Outcome of interest Can we be confident that the outcome of interest was not present at start of study?	Confounding-assessment Can we be confident in the assessment of confounding factors?	Confounding-analysis Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?	Assessment of outcome Can we be confident in the assessment of outcome?	Follow up Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?	Co-interventions Were co-interventions similar between groups?	Overall Risk of bias

	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Low, Some concerns, High
Anderson, 2018	*Definitely yes* Reason: Participants were selected from the NIS dataset	*Probably yes* Reason: Definition of high- and low-volume was obtained from own data using logistic regression with Restricted Cubic Splines	*Probably yes* Reason: Outcome data were obtained from the registry	*Probably yes* Reason: Confouding factors were described and obtained from the dataset.	*Probably yes* Reason: A priori covariates were defined. There was adjustment for covariates in the multivariate logistic regression	*Definetly yes* Reason: Outcomes were defined according to ICD-9 diagnoses and procedure codes	*Probably no* Reason: Follow up period was not specified or reported	*No information* Reason: No information regarding type of surgery or other co-interventions	**Some concerns (regarding follow-up and co-interventions)**
Barac Nekic, 2022	*Definitely yes* Reason: Participants were drawn from the Croatian ACC registry	*Probably no* Reason: No clear definition of low-volume surgeries	*Probably yes* Reason: Outcome data were obtained from the registry	*Probably yes* Reason: Confouding factors were described and obtained from the dataset.	*Probably yes* Reason: Regarding outcome recurrence-free survival there was adjustment for confounding factors	*Definetly yes* Reason: Clear definition regarding recurrence-free survival	*Probably yes* Reason: Follow-up period was specified, no missing data reported.	*Probably no* Reason: Co-intervention adjuvant therapy is reported but not similar between groups (60% vs. 42.9%) and no correction in multivariate analysis	**Some concerns (regarding assessment of exposure and co-interventions)**
Bergamini, 2011	*Definitely yes* Reason: Participants were drawn from the IRES-A registry	*Probably yes* Reason: Clear definition regarding referral and non-referral centers	*Probably yes* Reason: Outcome data were obtained from the registry	*Probably no* Reason: Confounding factors were not specified or described, no baseline characteristich for subgroups	*Probably no* Reason: There was no (statistical) adjustment for confounding factors	*Probably yes* Reason: Clear definitions of outcomes (complications)	*Probably no* Reason: Follow up period was not specified or reported	*Probably no* Reason: No information regarding type of surgery or other co-interventions	**High (regarding confounding, follow up and co-interventions)**

				referral and non-referral					
Gratian, 2014	*Definitely yes* Reason: Participant data was drawn from NHS data	*Probably yes* Reason: Clear definition regarding high-volume surgeons	*Probably yes* Reason: Outcome data were obtained from the database	*Probably yes* Reason: Confounding factors were prespecified, obtained from the database.	*Probably yes* Reason: There was statistical adjustment for confounding factors for the primary and secondary outcomes	*Definetly yes* Reason: Clear definition outcomes	*Probably yes* Reason: Follow-up was specified and adequate for outcome (5-year OS). Missing outcome data was imputed	*No information* Reason: Co-interventions (chemotherapy, radiotherapy) were reported but not clear if there was adjustment for these factors in multivariate analysis	**Some concerns (regarding co-interventions)**
Gray, 2021	*Probably no* Reason: Participant data was drawn from National Cancer Data Base but no clear in- and exclusion criteria and no characteristics available for high- and low-volume surgical group	*Probably yes* Reason: Clear definition regarding high- and low-volume centers	*Probably yes* Reason: Outcome data were obtained from the database	*Probably yes* Reason: Confounding factors (baseline characteristics) were described and obtained from the data base	*Probably yes* Reason: There was statistical adjustment for confounding factors for the primary outcome	*Definetly yes* Reason: Clear definition of primary outcome (overall survival)	*Probably no* Reason: Follow up period was not specified or reported	*No information* Reason: No information	**Some concerns (participant selection and follow-up)**
Greco, 2011	*Probably no* Reason: Database with data from questionnaires of 23 urological departments (only urological)	*Probably yes* Reason: Clear definition regarding experience of laparoscopic adrenalectomies	*Probably yes* Reason: Outcome data were obtained from the questionnaires	*Probably yes* Reason: Confounding factors (baseline characteristics) were described and obtained	*Probably no* Reason: There was no statistical adjustment for confounding factors	*Probably yes* Reason: No exact definition of primary outcome measure (hospital stay)	*Probably no* Reason: There was no follow-up period specified. Missing or incomplete data were not reported	*Probably no* Reason: Regarding the outcome hospital stay relevant co-interventions were reported (but no statistical	**High (regarding selection of participants, confoundin, follow-up and co-interventions)**

				from the questionnaires				adjustment in analysis) for difference in treatment groups	
Hermsen, 2012	*Definitely no* Reason: The database only contains patients who have been treated in a DAN center at any time during course of disease	*Probably yes* Reason: Clear definition of DAN or non-DAN hospitals	*Probably yes* Reason: Outcome data were obtained from the database	*Probably yes* Reason: Confounding factors (baseline characteristics) were described and obtained from database	*Probably yes* Reason: There was statistical adjustment for confounding factors for the primary outcome	*Probably yes* Reason: No exact definition of primary outcome (overall survival)	*Probably yes* Reason: Follow-up period was specified and adequate for primary outcome (overall survival). Only incomplete outcome data for resection status reported	*Probably yes* Reason: Relevant co-interventions (adjuvant therapy) were reported, not clear if co-interventions are similar between groups	**Some concerns (regarding participant selection and co-interventions)**
Kerkhofs, 2013	*Probably yes* Reason: Netherlands Cancer Registry database	*Probably yes* Reason: Clear definition of DAN or non-DAN hospitals	*Probably yes* Reason: Outcome data were obtained from the database	*Probably yes* Reason: Confounding factors (baseline characteristics) were described and obtained from database	*Probably yes* Reason: There was statistical adjustment for confounding factors	*Probably yes* Reason: No exact definition of primary outcome (overall survival)	*Probably yes* Reason: Follow-up period was specified and adequate for primary outcome (overall survival). Loss-to-follow-up data was reported	*No information* Reason: No information regarding relevant co-interventions (adjuvant therapy, non-surgery) or similarity in treatment groups	**Some concerns (regarding co-interventions)**
Lombardi, 2012	*Probably yes* Reason: Multi-institutional survey data	*Probably yes* Reason: Clear definition of high- and low-volume centers	*Probably yes* Reason: Outcome data were obtained from the database	*Probably yes* Reason: Confounding factors (baseline characteristics) were described and obtained from database	*Probably yes* Reason: There was statistical adjustment for confounding factors	*Definetly yes* Reason: Clear definition of primary outcome (overall survival)	*Probably yes* Reason: Follow-up period was specified and adequate for primary outcome (overall survival). Loss-to-follow-up data was reported	*Probably no* Reason: Co-interventions (laparoscopic resection and adjuvant therapy) were significantly different between treatment groups.	**Some concerns (regarding co-interventions)**

MacKinney, 2022	*Probably yes* Reason: Participant data was drawn from National Cancer Data Base	*Probably yes* Reason: Clear definition of high- and low-volume centers	*Probably yes* Reason: Outcome data were obtained from the database	*Probably yes* Reason: Confounding factors (baseline characteristics) were described and obtained from database	*Probably yes* Reason: There was statistical adjustment for confounding factors	*Probably yes* Reason: No exact definition of primary outcome (survival)	*Probably no* Reason: No length of follow-up or handling of missing data were reported	*Probably no* Reason: Co-interventions (surgery and adjuvant therapy) were significantly different between treatment groups.	**Some concerns (regarding follow-up and co-interventions**

Table of excluded studies

Reference	Reason for exclusion
Langenhuijsen J, Birtle A, Klatte T, Porpiglia F, Timsit MO. Surgical Management of Adrenocortical Carcinoma: Impact of Laparoscopic Approach, Lymphadenectomy, and Surgical Volume on Outcomes-A Systematic Review and Meta-analysis of the Current Literature. Eur Urol Focus. 2016 Feb;1(3):241-250. doi: 10.1016/j.euf.2015.12.001. Epub 2015 Dec 24. Erratum in: Eur Urol Focus. 2018 Apr;4(3):461. PMID: 28723392.	Separate studies from systematic review were included
Palazzo F, Dickinson A, Phillips B, Sahdev A, Bliss R, Rasheed A, Krukowski Z, Newell-Price J. Adrenal surgery in England: better outcomes in high-volume practices. Clin Endocrinol (Oxf). 2016 Jul;85(1):17-20. doi: 10.1111/cen.13021. Epub 2016 Feb 15. PMID: 26776382.	Same database was used as included study (Gray, 2021)
Al-Qurayshi Z, Robins R, Buell J, Kandil E. Surgeon volume impact on outcomes and cost of adrenal surgeries. Eur J Surg Oncol. 2016 Oct;42(10):1483-90. doi: 10.1016/j.ejso.2016.06.392. Epub 2016 Jun 23. PMID: 27378161.	Same database was used as included study (Anderson, 2018)
Park HS, Roman SA, Sosa JA. Outcomes from 3144 adrenalectomies in the United States: which matters more, surgeon volume or specialty? Arch Surg. 2009 Nov;144(11):1060-7. doi: 10.1001/archsurg.2009.191. PMID: 19917944.	Same database was used as included study (Anderson, 2018)
Hauch A, Al-Qurayshi Z, Kandil E. Factors associated with higher risk of complications after adrenal surgery. Ann Surg Oncol. 2015 Jan;22(1):103-10. doi: 10.1245/s10434-014-3750-2. Epub 2014 May 3. PMID: 24793341.	Same database was used as included study (Anderson, 2018)
Fassnacht M, Johanssen S, Fenske W, Weismann D, Agha A, Beuschlein F, Führer D, Jurowich C, Quinkler M, Petersenn S, Spahn M, Hahner S, Allolio B; German ACC Registry Group. Improved survival in patients with stage II adrenocortical carcinoma followed up prospectively by specialized centers. J Clin Endocrinol Metab. 2010 Nov;95(11):4925-32. doi: 10.1210/jc.2010-0803. Epub 2010 Jul 28. PMID: 20668036.	No specific comparison between care in high- and low-volume centers

Literature search strategy

Algemene informatie

Richtlijn: NVvH bijniertumoren	
Uitgangsvraag: Wat is de waarde van een expertise- of hoog-volumecentrum voor bijnierchirurgie bij patiënten met een adrenocorticaal carcinoom of een vermoeden daarvan?	
Database(s): Ovid/Medline, Embase	Datum: 1-3-2022
Periode: 2000-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende elementen: (Adrenalectomy of adrenocorticaal carcinoma of adrenal cancer) EN (expertise centra of high volume) Met uitzondering van het artikel van Grubbs, worden alle sleutelartikelen gevonden. Het artikel van Grubbs wordt niet gevonden omdat het over de vergelijking chirurgie versus chirurgie + mitotane gaat en niet over de expertisecentra.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 1-3-2022 met relevante zoektermen gezocht naar systematische reviews en RCTs over expertise- of hoog-volumecentrum voor bijnierchirurgie bij patiënten met een adrenocorticaal carcinoom of een vermoeden daarvan. De literatuurzoekactie leverde 283 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	19	10	20
RCTs	6	5	8
Observationele studies	203	155	255
Overig			
Totaal			283

Zoekstrategie

Embase

No.	Query	Results
#25	#9 NOT #24	2
#24	#9 AND #23	6
#23	#18 OR #19 OR #20	228
#22	#20 NOT #19 NOT #18 OBS	203

No.	Query	Results
#21	#19 NOT #18 RCT	6
#20	#13 AND (#16 OR #17)	216
#19	#13 AND #15	7
#18	#13 AND #14 SR	19
#17	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	12922469
#16	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6935197
#15	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1880869
#14	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	803979
#13	#12 AND [1-1-2000]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	307
#12	#10 AND #11	470
#11	'high volume hospital'/exp OR 'low volume hospital'/exp OR 'high volume surgeon'/exp OR 'patient volume'/exp OR 'cooperation'/exp OR (((central* OR special* OR exper* OR volume OR dan) NEAR/3 (hospital* OR center* OR centres*)):ti,ab,kw) OR 'dan hospital*':ti,ab,kw OR ((central* NEAR/3 surg*):ti,ab,kw)	211723

No.	Query	Results
#10	'adrenal cortex carcinoma'/exp OR 'adrenalectomy'/exp OR 'adrenal cancer'/exp OR 'suprarenal carcinoma':ti,ab,kw OR (((adren* OR suprarenal) NEAR/4 (cancer* OR neoplasm* OR carcinoma*)):ti,ab,kw) OR 'adrenal enucleation':ti,ab,kw OR 'hemiadrenalectomy':ti,ab,kw	42320
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	8
#8	recurrence AND of AND adrenal AND cortical AND carcinoma AND following AND resection AND alone A ND can AND achieve AND results AND equal AND to AND surgery AND plus AND mitotane AND grubbs	1
#7	. AND improved AND survival AND in AND patients AND with AND stage AND ii AND adrenocortical AND carcinoma AND followed AND up AND prospectively AND by AND specialized AND centers AND fassnacht	1
#6	effect AND surgeon AND expertise AND on AND the AND outcome AND of AND patients AND with AND a drenocortical AND carcinoma	1
#5	treatment AND patterns AND outcomes AND for AND patients AND adrenocortical AND carcinoma AND associated AND with AND hospital AND case AND volume AND in AND the AND united AND states AND g ratian AND 2014	1
#4	outcomes AND from AND 3144 AND adrenalectomies AND in AND the AND united AND states AND park AND 2009	1
#3	adrenocortical AND carcinoma AND effect AND of AND hospital AND volume AND on AND patient AND o utcome AND lombardi AND 2012	1
#2	surgery AND for AND adrenocortical AND carcinoma AND in AND the AND netherlands AND kerkhofs AN D 2013 NOT berruti NOT zwan	1
#1	surgery AND in AND adrenocortical AND carcinoma AND importance AND of AND national AND cooperat ion AND centralized AND surgery.	1

Ovid/Medline

#	Searches	Results
17	13 not 12 not 11 OBS	155
16	12 not 11 RCT	5
15	1 and 14	1
14	11 or 12 or 13	170
13	6 and (9 or 10)	162
12	6 and 8	6
11	6 and 7 SR	10
10	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5092813
9	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4078955
8	(exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/)	1354591

7	(meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	549449
6	5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	243
5	limit 4 to yr="2000 -Current"	249
4	2 and 3	273
3	Hospitals, High-Volume/ or Hospitals, Low-Volume/ or Hospitals, Special/ or Surgicenters/ or ((central* or special* or exper* or volume or dan) adj3 (hospital* or center* or centres*)).ti,ab,kf. or dan hospital*.ti,ab,kf. or (central* adj3 surg*).ti,ab,kf.	97289
2	Adrenalectomy/ or exp Adrenal Gland Neoplasms/ or suprarenal carcinoma.ti,ab,kf. or ((adren* or suprarenal) adj4 (cancer* or neoplasm* or carcinoma*)).ti,ab,kf. or adrenal enucleation.ti,ab,kf. or hemiadrenalectomy.ti,ab,kf.	48470
1	"The effect of surgeon expertise on the outcome of patients with adrenocortical carcinoma" [Article Title]	1

Module 8 – Biopsie bij ongedefinieerde retroperitoneale massa

Uitgangsvraag
Wat is de diagnostische accuratesse en wat zijn de risico's van een CT-geleid biopt in het diagnostisch traject bij patiënten met een ongedefinieerde retroperitoneale massa die radiologisch uit lijkt te gaan van de bijnier?

Inleiding
Wanneer een retroperitoneale tumor mogelijk uitgaande van de bijnier middels beeldvorming wordt vastgesteld, zal de differentiaaldiagnose een primaire bijniertumor (goedaardig of kwaadaardig), een metastase of een tumor uitgaande van ander weefsel (bijvoorbeeld lymfoom, sarcoom niercelcarcinoom) betreffen. Andere redenen voor bijniervergroting zijn inclusief: metabole stoornissen, stapelingsziekten, spontane bloeding of inflammatie/infectie.

De differentiaaldiagnose van de primaire bijniertumoren kan voor het merendeel via de kliniek, middels verschillende radiologische en nucleaire geneeskundige technieken en biochemische testen vastgesteld worden. In geval van metastasen is er in de grote meerderheid van de gevallen een primaire tumor bekend. De diagnose metastase is met aanvullende diagnostiek (radiologie, nucleair geneeskundige en evt. middels biochemie uitsluiten primaire bijniertumor) goed te stellen. De overige boven gemelde diagnoses zijn zeldzaam. Zo is een bloeding via de kliniek en met radiologisch onderzoek vast te stellen en zullen stapelingsziekten en inflammatie via andere onderzoeken diagnosticeerd worden (klinisch en biochemisch).

Bij sommige patiënten, kan er, ondanks alle relevante niet-invasieve onderzoeken (verschillende scans en laboratorium onderzoek) nog geen diagnose zijn vastgesteld en kan het zijn dat in een dergelijke situatie een biopt wordt geadviseerd na beoordeling van de casus in een multidisciplinair overleg (endocrien en/of bijnier MDO) dat bestaat uit de relevante experts. Een biopt van een bijniertumor, of tumor daarnaast, is geassocieerd met bepaalde risico's en ook met een lage sensitiviteit voor bijnierschorscarcinoom. Dus de diagnostische nauwkeurigheid en de kans voor het optreden van complicaties zijn relevante overwegingen binnen de besluitvorming in het multidisciplinaire team en zijn de focus van deze module.

Search and select
A systematic review of the literature was performed to answer the following questions: What is the diagnostic performance of CT guided biopsy in patients with an atypical retroperitoneal mass in or near to the adrenal gland which has not been diagnosed with adequate certainty by non-invasive imaging and laboratory tests? And what are the complications, including the risk of tumor seeding?

P (Patients)	patients with an atypical retroperitoneal mass in or near the adrenal gland, undiagnosable after prior imaging and laboratory testing (CT, MRI, PET/CT, biochemistry etc.)
I (Intervention)	CT guided biopsy
C (Control)	non-invasive investigation (no CT guided biopsy)
R (Reference)	pathology after surgery, follow-up
O (Outcomes)	diagnostic accuracy (other tumor in the region; sensitivity, specificity, positive predictive value, negative predictive value, area under the ROC curve), complications (including risk of tumor seeding)

T (Timing)	in the diagnostic phase (before definitive treatment)
S (Setting)	in the hospital

Relevant outcome measures
The guideline development group considered diagnostic accuracy (other tumor in the region) and complications (e.g. bleeding) as critical outcome measures for decision making.

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

Table 1 - consequences of diagnostic test properties

Outcome	Consequence
True positives (TP)	Patient has a tumor and the tumor is correctly identified, the patient will get the appropriate treatment
True negatives (TN)	Patient is correctly identified as not having a tumor and will be managed appropriately
False positives (FP)	Patient is wrongly diagnosed with a tumor, with a risk of getting inappropriate treatment
False negatives (FN)	Patient is incorrectly diagnosed as not having a tumor, with a risk of getting inappropriate treatment
Inconclusive outcome	No diagnosis made, with the result that further investigation is needed and diagnostic delay is possible

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until 08-02-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 268 hits. Studies were selected based on the following criteria:

- Systematic reviews, randomized controlled trials, or observational comparative studies;
- Full-text English or Dutch language publication;
- Complying with the PICROTS criteria.

Fifty-eight studies were initially selected based on title and abstract screening. After reading the full text, 58 studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Results
No studies were included in the analysis of the literature.

Summary of literature

Description of studies
Not applicable.

Results
Diagnostic accuracy, complications
No studies were found that directly compared CT guided biopsy with no biopsy in patients with an atypical retroperitoneal mass in the adrenal lodge, undiagnosable after prior imaging, on the outcomes: diagnostic accuracy and complications.

Level of evidence of the literature

Diagnostic accuracy, complications

The level of evidence for the comparison CT guided biopsy versus no biopsy could not be assessed for the outcomes diagnostic accuracy and complications since no appropriate studies were found.

Conclusions

Diagnostic accuracy, complications

- **GRADE**	No evidence was found specifically comparing CT guided biopsy with no biopsy in the diagnostic trajectory of patients with an atypical retroperitoneal mass in the adrenal lodge, not diagnosed after prior imaging and laboratory investigations. *Source: -*

Overwegingen – van bewijs naar aanbeveling

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

Het is tot op heden onduidelijk wat de rol van CT-geleide biopsie is in het diagnostisch traject bij patiënten met een ongedefinieerde retroperitoneale massa mogelijk uitgaande van de bijnier. Literatuuronderzoek leverde geen studies op die een directe vergelijking maakten tussen een CT-geleide biopsie en geen biopsie waarin de diagnostische accuratesse of complicaties (inclusief tumor seeding) werden gerapporteerd. Rekening houdend met het gebrek aan vergelijkende data, hebben we vervolgens gekeken naar een systematic review (Bancos, 2016) waarin 32 studies met 2174 patiënten waren opgenomen. In deze studie werd gekeken naar de diagostische accuratesse, het optreden van complicaties en de frequentie van niet-diagnostische puncties. In 8.7% (95%CI: 6-11%) van 2013 biopsien was er sprake van een niet-diagnostische punctie. In 2.5% (95%CI:1.5-3.4%) was er sprake van een complicatie. Dit getal is waarschijnlijk een onderschatting onder andere vanwege het retrospectieve karakter van de studies. De diagnose maligniteit (in 8 studies) werd beschreven met een sensitiviteit van 87% en specificiteit van 100%. Voor metastasen was de sensitiviteit hoger (87%) dan voor bijnierschorscarcinoom (70%).

Andere primaire tumoren die in de bijnierloge kunnen voorkomen zijn bijvoorbeeld een weke delen tumor ofwel sarcoom. Voor een (retroperitoneaal) sarcoom moet soms ook een neoadjuvante therapie kunnen worden overwogen, daarom is een biopsie voor het stellen van die diagnose belangrijk. Het biopteren van een weke delen tumor/sarcoom is veilig en geeft geen verhoogd risico op lokaal recidief (Wilkinson, 2015). Bovendien is tumorseeding door biopsie zeer zeldzaam (Berger-Richardson, 2017). Dit geldt eveneens voor het pathologisch vaststellen van andere tumoren in de bijnierloge zoals bijvoorbeeld een maligne lymfoom. Het doen van een biopsie in bovenstaande situaties wordt bij voorkeur gedaan na bespreking in een bijniertumoren MDO of ander relevant MDO met consultatie van bijnier experts.

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

De beslissing om een biopsie te doen zal door de arts, vaak na overleg in een MDO, moeten worden genomen. Deze kan de afwegingen maken wat de risico's zijn bij de biopsie en wat de consequentie kan zijn voor de uitkomsten van de eventuele biopsie. Die kennis zal gedeeld moeten worden met de patiënt zodat hij/zij goed geïnformeerd is over de overwegingen en het besluit van wel of niet biopsie.

Kosten (middelenbeslag)
Een biopsie is zelden nodig in geval van een tumor in de bijnier en de kosten van een ongecompliceerde procedure zijn als laag te beschouwen. Wanneer de indicatie bestaat zal het biopt gedaan worden om een specifieke diagnose te stellen en gerichte therapie te kunnen geven. Hiermee wordt kosteneffectief gehandeld.

Aanvaardbaarheid, haalbaarheid en implementatie
De indicatie voor een biopsie in een tumor in de bijnier(loge) is zeldzaam. Met kennis van de richtlijn en de overwegingen zal er draagvlak zijn om de richtlijn te volgen. Het risico is gelegen in het gegeven dat er situaties zullen zijn dat er een tumor wordt gezien in een bijnier, bij toeval gevonden en er waarborging van good practice besloten wordt tot een biopsie. Een advies door radioloog en/of clinicus om de patiënt met de gevonden tumor eerst in een multidisciplinair overleg (MDO) binnen een expertisecentrum te bespreken kan helpen dit risico te reduceren.

Aanbeveling
Rationale van de aanbeveling: weging van argumenten voor en tegen de diagnostische procedure
Wanneer klinisch en biochemisch een bijnierschorscarcinoom of een feochromocytoom is bewezen, of aan zekerheid grenzende waarschijnlijkheid is vastgesteld, wordt een biopsie afgeraden, maar een behandeling volgens de richtlijn van die diagnose, in het algemeen een operatie. Wanneer een goedaardige aandoening van een bijniertumor met non-invasieve functionele diagnostiek is vastgesteld, is een biopsie van die aandoening eveneens niet aangewezen. Echter, wanneer een grote bijnier tumor van onbekende origine in de bijnierloge wordt aangetoond met op beeldvorming met maligne kenmerken en functioneel niet typisch voor een diagnose, kan een radiologisch gestuurd biopt worden aangeraden om een andere diagnose dan ACC aan te tonen wanner verwacht wordt dat dit behandeling beïnvloedt. Voorbeelden zijn het vaststellen van metastasen van andere primaire tumoren met behandelconsequenties, of het vaststellen van een andere primaire tumor, zoals bijvoorbeeld een sarcoom om te voorkomen dat de patiënt in het verkeerde behandeltraject terecht komt.

Biopteer een tumor in de bijnier(loge) alleen indien:
1. een feochromocytoom is uitgesloten *en*
2. een verdenking bijnierschorscarcinoom of benigne tumor niet al op andere gronden (klinisch, biochemisch, beeldvorming) is vastgesteld (conform module 'Diagnostiek bijnier incidentaloom') *en*
3. verwacht wordt dat de uitkomst van het biopt klinische behandelconsequenties heeft *en*
4. dit vooraf besproken is in een multidisciplinair overleg (endocrien en/of bijnier MDO).

Literatuur

Bancos I, Tamhane S, Shah M, Delivanis DA, Alahdab F, Arlt W, Fassnacht M, Murad MH. DIAGNOSIS OF ENDOCRINE DISEASE: The diagnostic performance of adrenal biopsy: a systematic review and meta-analysis. Eur J Endocrinol. 2016 Aug;175(2):R65-80. doi: 10.1530/EJE-16-0297. Epub 2016 Jun 2. PMID: 27257146.

Berger-Richardson D, Swallow CJ. Needle tract seeding after percutaneous biopsy of sarcoma: Risk/benefit considerations. Cancer. 2017 Feb 15;123(4):560-567. doi: 10.1002/cncr.30370. Epub 2016 Nov 2. PMID: 27859013.

Wilkinson MJ, Martin JL, Khan AA, Hayes AJ, Thomas JM, Strauss DC. Percutaneous core needle biopsy in retroperitoneal sarcomas does not influence local recurrence or overall survival. Ann Surg Oncol. 2015 Mar;22(3):853-8. doi: 10.1245/s10434-014-4059-x. Epub 2014 Sep 5. PMID: 25190132.

Bijlagen bij module Biopsie bij ongedefinieerde retroperitoneale massa

Evidencetabellen
Niet van toepassing.

Table of excluded studies

Reference	Reason for exclusion
Luca Alatzides G, Luisa Steinberg H, Schildhaus HU, Hamacher R, Kaths M, Grueneisen J, Treckmann J, Bauer S, Umutlu L, Schaarschmidt B. Is preoperative CT-guided biopsy a valuable tool in the diagnostic workup of patients with visceral and retroperitoneal sarcoma? Eur J Radiol. 2022 Oct;155:110470. doi: 10.1016/j.ejrad.2022.110470. Epub 2022 Aug 10. PMID: 35985092.	Wrong P (suspected soft tissue sarcoma)
Albertsmeier M, Lindner LH, Werner J, Angele MK. Wann Biopsie, wann primäre Resektion? [Initial management of a suspected retroperitoneal soft tissue tumor - biopsy vs. primary resection]. MMW Fortschr Med. 2017 Oct;159(18):60-64. German. doi: 10.1007/s15006-017-0178-1. PMID: 29071612.	Full-text unavailable, article in German
Alguraan Z, Agcaoglu O, El-Hayek K, Hamrahian AH, Siperstein A, Berber E. Retroperitoneal masses mimicking adrenal tumors. Endocr Pract. 2012 May-Jun;18(3):335-41. doi: 10.4158/EP11240.OR. PMID: 22068255.	Wrong study design (case series)
Almond LM, Tirotta F, Tattersall H, Hodson J, Cascella T, Barisella M, Marchianò A, Greco G, Desai A, Ford SJ, Gronchi A, Fiore M, Morosi C. Diagnostic accuracy of percutaneous biopsy in retroperitoneal sarcoma. Br J Surg. 2019 Mar;106(4):395-403. doi: 10.1002/bjs.11064. Epub 2019 Jan 24. PMID: 30675910.	Wrong P (suspected retroperitoneal sarcoma)
Anand D, Barroeta JE, Gupta PK, Kochman M, Baloch ZW. Endoscopic ultrasound guided fine needle aspiration of non-pancreatic lesions: an institutional experience. J Clin Pathol. 2007 Nov;60(11):1254-62. doi: 10.1136/jcp.2006.045955. Epub 2007 Jan 12. PMID: 17220205; PMCID: PMC2095489.	Wrong/no comparison as in the PICROTS
Avancès C, Camparo P, Quenet F, Durand X, Culine S, Sèbe P, Soulié M, Rigaud J; Comité de Cancérologie de l'Association Française d'Urologie - groupe Organes Génitaux Externes (CCAFU-OGE). Histoire naturelle et prise en charge des sarcomes du rétropéritoine : état des lieux par le comité de cancérologie de l'association française d'urologie sous comité Organes génitaux externes [Natural history and management of retroperitoneal sarcoma: Review of the literature by the Oncology committee of the French association of urology]. Prog Urol. 2011 Jul;21(7):441-7. French.	Full-text unavailable, article in French

doi: 10.1016/j.purol.2010.09.029. Epub 2011 Apr 14. PMID: 21693353.	
Chander, R., Singh, S., Singh, A., & Singh, B. (2014). Role of Spiral Computed Tomography Scan in Evaluation of Retroperitoneal Pathologies. JK Science, 16(1), 11.	Wrong I (CT scan)
Chew C, Reid R, O'Dwyer PJ. Value of biopsy in the assessment of a retroperitoneal mass. Surgeon. 2006 Apr;4(2):79-81. doi: 10.1016/s1479-666x(06)80034-x. PMID: 16623162.	Wrong/no comparison as in the PICROTS
Chhieng DC, Jhala D, Jhala N, Eltoum I, Chen VK, Vickers S, Heslin MJ, Wilcox CM, Eloubeidi MA. Endoscopic ultrasound-guided fine-needle aspiration biopsy: a study of 103 cases. Cancer. 2002 Aug 25;96(4):232-9. doi: 10.1002/cncr.10714. PMID: 12209665.	Wrong/no comparison as in the PICROTS
Chojniak R, Isberner RK, Viana LM, Yu LS, Aita AA, Soares FA. Computed tomography guided needle biopsy: experience from 1,300 procedures. Sao Paulo Med J. 2006 Jan 5;124(1):10-4. doi: 10.1590/s1516-31802006000100003. Epub 2006 Apr 3. PMID: 16612456.	Wrong/no comparison as in the PICROTS
Chung AD, Krishna S, Schieda N. Primary and secondary diseases of the perinephric space: an approach to imaging diagnosis with emphasis on MRI. Clin Radiol. 2021 Jan;76(1):75.e13-75.e26. doi: 10.1016/j.crad.2020.06.022. Epub 2020 Jul 22. PMID: 32709392.	Wrong study design (non-systematic review)
Daneshmand S, Youssefzadeh D, Chamie K, Boswell W, Wu N, Stein JP, Boyd S, Skinner DG. Benign retroperitoneal schwannoma: a case series and review of the literature. Urology. 2003 Dec;62(6):993-7. doi: 10.1016/s0090-4295(03)00792-1. PMID: 14665342.	Wrong study design (case series)
Das A, Gahine R, Patre V, Hussain N. Retroperitoneal Tumor: A Silent Trespasser - Role of Image-Guided Fine-Needle Aspiration Cytology with Histopathological Correlation in Early Diagnosis. Acta Cytol. 2019;63(3):189-197. doi: 10.1159/000497077. Epub 2019 Mar 20. PMID: 30893686.	Wrong P (only a few adrenal retroperitoneal masses)
Das C, Sengupta M, Mukhopadhyay M, Saha AK. Critical clinical appraisal of the role of computed tomography-guided minimally invasive aspiration cytology in evaluation of retroperitoneal masses. Indian J Med Paediatr Oncol. 2014 Jan;35(1):60-5. doi: 10.4103/0971-5851.133723. PMID: 25006286; PMCID: PMC4080665.	Wrong/no comparison as in the PICROTS
De Filippo M, Saba L, Azzali E, Milanese G, Mostardi M, Borgia D, Capasso R, Nizzoli R. CT-guided fine-needle aspiration of abdominal and retroperitoneal small lesions with the coaxial technique using MPR	Wrong/no comparison as in the PICROTS

images. Acta Biomed. 2016 Jul 28;87 Suppl 3:57-62. PMID: 27467869.	
De Filippo M, Saba L, Rossi E, Nizzoli R, Tiseo M, Pedrazzi G, Brunese L, Rotondo A, Rossi C. Curved Needles in CT-Guided Fine Needle Biopsies of Abdominal and Retroperitoneal Small Lesions. Cardiovasc Intervent Radiol. 2015 Dec;38(6):1611-6. doi: 10.1007/s00270-015-1107-2. Epub 2015 Apr 25. PMID: 25910970.	Wrong/no comparison as in the PICROTS
Wu, D., Ding, X., & Chen, K. (2006). CT-guided biopsy of malignant lymphoma. Journal of Interventional Radiology, 15(1), 25-27.	Full-text unavailable.
Dvorak P, Hoffmann P, Balik M, Hoffmannova M, Kopecky J, Dvorakova R, Nova M. Percutaneous biopsy of retroperitoneal lesions - 10 year experience of a single centre. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2020 Dec;164(4):435-443. doi: 10.5507/bp.2019.028. Epub 2019 Jun 17. PMID: 31219106.	Wrong/no comparison as in the PICROTS
Erickson RA, Tretjak Z. Clinical utility of endoscopic ultrasound and endscopic ultrasound-guided fine needle aspiration in retroperitoneal neoplasms. Am J Gastroenterol. 2000 May;95(5):1188-94. doi: 10.1111/j.1572-0241.2000.02008.x. PMID: 10811326.	Wrong P (nonadrenal)
Feng Y, Zhang W, Luo C. Evaluation of clinical application of multi-slice computerized tomography in primary retroperitoneal tumors. J Clin Lab Anal. 2020 May;34(5):e23169. doi: 10.1002/jcla.23169. Epub 2019 Dec 27. PMID: 31880021; PMCID: PMC7246388.	Non-diagnostic (already diagnosed with retroperitoneal tumor)
Guo Z, Kurtycz DF, De Las Casas LE, Hoerl HD. Radiologically guided percutaneous fine-needle aspiration biopsy of pelvic and retroperitoneal masses: a retrospective study of 68 cases. Diagn Cytopathol. 2001 Jul;25(1):43-9. doi: 10.1002/dc.2000. PMID: 11466812.	Wrong/no comparison as in the PICROTS
Gupta P, Rajwanshi A, Nijhawan R, Srinivasan R, Gupta N, Saikia UN, Dey P. Fine needle aspiration in retroperitoneal lesions. APMIS. 2017 Jan;125(1):16-23. doi: 10.1111/apm.12627. Epub 2016 Nov 2. PMID: 27807894.	Wrong/no comparison as in the PICROTS
Gupta RK, Cheung YK, alAnsari AG, Naran S, Lallu S, Fauck R. Value of image-guided needle aspiration cytology in the assessment of pelvic and retroperitoneal masses. A study of 112 cases. Acta Cytol. 2003 May-Jun;47(3):393-8. doi: 10.1159/000326539. PMID: 12789920.	Wrong/no comparison as in the PICROTS
Han C, Lin R, Zhang Q, Liu J, Ding Z, Hou X. Role of endoscopic ultrasound-guided fine needle aspiration in the diagnosis of mass lesions. Exp Ther Med. 2016 Aug;12(2):1085-1092. doi: 10.3892/etm.2016.3433.	Wrong/no comparison as in the PICROTS

Epub 2016 Jun 7. PMID: 27446324; PMCID: PMC4950895.	
Hwang SY, Warrier S, Thompson S, Davidson T, Yang JL, Crowe P. Safety and accuracy of core biopsy in retroperitoneal sarcomas. Asia Pac J Clin Oncol. 2016 Mar;12(1):e174-8. doi: 10.1111/ajco.12125. Epub 2013 Oct 31. PMID: 24176000.	Wrong P (sarcoma)
Ikoma N, Torres KE, Somaiah N, Hunt KK, Cormier JN, Tseng W, Lev D, Pollock R, Wang WL, Feig B. Accuracy of preoperative percutaneous biopsy for the diagnosis of retroperitoneal liposarcoma subtypes. Ann Surg Oncol. 2015 Apr;22(4):1068-72. doi: 10.1245/s10434-014-4210-8. Epub 2014 Oct 30. PMID: 25354575; PMCID: PMC4520392.	Wrong P (liposarcoma)
Ishikawa T, Mohamed R, Heitman SJ, Turbide C, Kumar PR, Goto H, Hirooka Y, Belletrutti PJ. Diagnostic yield of small histological cores obtained with a new EUS-guided fine needle biopsy system. Surg Endosc. 2017 Dec;31(12):5143-5149. doi: 10.1007/s00464-017-5580-3. Epub 2017 May 10. PMID: 28493167.	Wrong/no comparison as in the PICROTS
Kaffes AJ, Chen RY, Tam W, Norton I, Cho S, Devereaux B, Vaughan R. A prospective multicenter evaluation of a new side-port endoscopic ultrasound-fine-needle aspiration in solid upper gastrointestinal lesions. Dig Endosc. 2012 Nov;24(6):448-51. doi: 10.1111/j.1443-1661.2012.01302.x. Epub 2012 Apr 8. PMID: 23078438.	Wrong/no comparison as in the PICROTS
Kariniemi J, Blanco Sequeiros R, Ojala R, Tervonen O. MRI-guided abdominal biopsy in a 0.23-T open-configuration MRI system. Eur Radiol. 2005 Jun;15(6):1256-62. doi: 10.1007/s00330-004-2566-z. Epub 2004 Dec 31. PMID: 15627187.	Wrong/no comparison as in the PICROTS
Kipp BR, Pereira TC, Souza PC, Gleeson FC, Levy MJ, Clayton AC. Comparison of EUS-guided FNA and Trucut biopsy for diagnosing and staging abdominal and mediastinal neoplasms. Diagn Cytopathol. 2009 Aug;37(8):549-56. doi: 10.1002/dc.21042. PMID: 19217057.	Wrong/no comparison as in the PICROTS
Koh, D. M., & Moskovic, E. (2000). Imaging tumours of the retroperitoneum. Imaging, 12(1), 49-60.	Wrong study design (non-systematic review)
Koike Y, Matsui S, Takase K, Tannai H. CT-Guided Percutaneous Needle Biopsy in Patients with Suspected Retroperitoneal Fibrosis: A Retrospective Cohort Study. Cardiovasc Intervent Radiol. 2019 Oct;42(10):1434-1440. doi: 10.1007/s00270-019-02266-x. Epub 2019 Jun 18. PMID: 31292673.	Wrong/no comparison as in the PICROTS
Lagos C C, Gallardo E, Huete Á. Biopsia percutánea core con aguja gruesa guiada por tomografía computada en lesiones retroperitoneales: Experiencia de 10 años [CT-guided core biopsy for retroperitoneal lesions. Experience in 136 procedures]. Rev Med Chil.	Full-text unavailable, article in Spanish

2019 Oct;147(10):1266-1272. Spanish. doi: 10.4067/s0034-98872019001001266. PMID: 32186634.	
Lai, J. H., Lin, H. H., Chen, M. J., & Lin, C. C. (2022). Safety and Effectiveness of Endoscopic Ultrasound-Guided Fine Needle Biopsy for Retroperitoneal and Gastrointestinal Tumors in Elderly Patients. International Journal of Gerontology, 16(3).	Wrong/no comparison as in the PICROTS
Li Q, Gao C, Juzi JT, Hao X. Analysis of 82 cases of retroperitoneal schwannoma. ANZ J Surg. 2007 Apr;77(4):237-40. doi: 10.1111/j.1445-2197.2007.04025.x. PMID: 17388825.	Wrong P (retroperitoneal Schwannoma)
Marcu, R. D., Diaconu, C. C., Constantin, T., Socea, B., Ionita-Radu, F., Mischianu, D. L. D., & Bratu, O. G. (2019). Minimally invasive biopsy in retroperitoneal tumors. Experimental and Therapeutic Medicine, 18(6), 5016-5020.	Wrong study design (non-systematic review)
Mazzaglia PJ, Monchik JM. Limited value of adrenal biopsy in the evaluation of adrenal neoplasm: a decade of experience. Arch Surg. 2009 May;144(5):465-70. doi: 10.1001/archsurg.2009.59. PMID: 19451490.	Wrong/no comparison as in the PICROTS
Merran, S., Karila-Cohen, P., & Vieillefond, A. (2004). Primary retroperitoneal tumors in adults. Journal de radiologie, 85(2 Pt 2), 252-264.	Full-text unavailable, article in French
Meyer S, Bittinger F, Keth A, Von Mach MA, Kann PH. Endosonographisch gesteuerte transluminale Feinnadelpunktion: Untersuchung zur diagnostischen Qualität [Endosonographically controlled transluminal fine needle aspiration biopsy: diagnostic quality by cytologic and histopathologic classification]. Dtsch Med Wochenschr. 2003 Jul 25;128(30):1585-91. German. doi: 10.1055/s-2003-40933. PMID: 12884145.	Full-text unavailable, article in German
Miyake M, Fukui S, Gotoh D, Matsumura Y, Samma S, Matsumoto Y, Momose H, Hori S, Watanabe S, Owari T, Morizawa Y, Itami Y, Nakai Y, Inoue T, Anai S, Torimoto K, Aoki K, Tanaka N, Fujimoto K. The diagnostic utility of retroperitoneoscopic tissue biopsy for unresectable retroperitoneal lesions excluding urogenital cancers. World J Surg Oncol. 2019 Feb 18;17(1):35. doi: 10.1186/s12957-019-1581-0. PMID: 30777073; PMCID: PMC6379945.	Wrong/no comparison as in the PICROTS
Morosi C, Stacchiotti S, Marchianò A, Bianchi A, Radaelli S, Sanfilippo R, Colombo C, Richardson C, Collini P, Barisella M, Casali PG, Gronchi A, Fiore M. Correlation between radiological assessment and histopathological diagnosis in retroperitoneal tumors: analysis of 291 consecutive patients at a tertiary reference sarcoma center. Eur J Surg Oncol. 2014	Wrong P (suspected retroperitoneal sarcoma)

Dec;40(12):1662-70. doi: 10.1016/j.ejso.2014.10.005. Epub 2014 Oct 15. PMID: 25454827.	
O'Connor K, Cheriyan DG, Li-Chang HH, Kalloger SE, Garrett J, Byrne MF, Weiss AA, Donnellan F, Schaeffer DF. Gastrointestinal Endoscopic Ultrasound-Guided Fine-Needle Aspiration Biopsy Specimens: Adequate Diagnostic Yield and Accuracy Can Be Achieved without On-Site Evaluation. Acta Cytol. 2015;59(4):305-10. doi: 10.1159/000439398. Epub 2015 Sep 5. PMID: 26339900.	Wrong/no comparison as in the PICROTS
Oldrini G, Leroux A, Vogin G, Rios M, Marchal F, Sirveaux F, Verhaeghe JL, Renard-Oldrini S, Lesanne G, Salleron J, Henrot P. Comparison of the histopathological results of the radioguided percutaneous microbiopsies and the operative specimens of soft tissue tumors of limbs, trunk and retroperitoneum. Presse Med. 2016 Nov;45(11):e363-e368. doi: 10.1016/j.lpm.2016.01.036. Epub 2016 Sep 3. PMID: 27597301.	Wrong/no comparison as in the PICROTS
Pham V, Henderson-Jackson E, Doepker MP, Caracciolo JT, Gonzalez RJ, Druta M, Ding Y, Bui MM. Practical Issues for Retroperitoneal Sarcoma. Cancer Control. 2016 Jul;23(3):249-64. doi: 10.1177/107327481602300308. PMID: 27556665.	Wrong P (retroperitoneal sarcoma)
Sauthier PG, Bélanger R, Provencher DM, Gauthier P, Drouin P. Clinical value of image-guided fine needle aspiration of retroperitoneal masses and lymph nodes in gynecologic oncology. Gynecol Oncol. 2006 Oct;103(1):75-80. doi: 10.1016/j.ygyno.2006.01.039. Epub 2006 Mar 10. PMID: 16530253.	Wrong P (gynecologic oncology)
Sood SK, Balasubramanian SP, Harrison BJ. Percutaneous biopsy of adrenal and extra-adrenal retroperitoneal lesions: beware of catecholamine secreting tumours! Surgeon. 2007 Oct;5(5):279-81. doi: 10.1016/s1479-666x(07)80026-6. PMID: 17958227.	Wrong study design (case series)
Spillane AJ. Retroperitoneal sarcoma: time for a change in attitude? ANZ J Surg. 2001 May;71(5):303-8. doi: 10.1046/j.1440-1622.2001.02109.x. PMID: 11374482.	Wrong study design (non-systematic review)
Stattaus J, Kalkmann J, Kuehl H, Metz KA, Nowrousian MR, Forsting M, Ladd SC. Diagnostic yield of computed tomography-guided coaxial core biopsy of undetermined masses in the free retroperitoneal space: single-center experience. Cardiovasc Intervent Radiol. 2008 Sep-Oct;31(5):919-25. doi: 10.1007/s00270-008-9317-5. Epub 2008 Mar 6. PMID: 18322731.	Wrong/no comparison as in the PICROTS
Strauss DC, Qureshi YA, Hayes AJ, Thomas JM. Management of benign retroperitoneal schwannomas: a single-center experience. Am J Surg.	Wrong P (Schwannoma)

2011 Aug;202(2):194-8. doi: 10.1016/j.amjsurg.2010.06.036. PMID: 21810500.	
Strauss DC, Hayes AJ, Thomas JM. Retroperitoneal tumours: review of management. Ann R Coll Surg Engl. 2011 May;93(4):275-80. doi: 10.1308/003588411X571944. PMID: 21944791; PMCID: PMC3363075.	Wrong study design (non-systematic review)
Tirotta F, Morosi C, Hodson J, Desai A, Barisella M, Ford SJ, Gronchi A, Almond LM, Fiore M. Improved Biopsy Accuracy in Retroperitoneal Dedifferentiated Liposarcoma. Ann Surg Oncol. 2020 Oct;27(11):4574-4581. doi: 10.1245/s10434-020-08519-1. Epub 2020 May 4. PMID: 32367501.	Wrong P (suspected primary retroperitoneal sarcoma)
Tomozawa Y, Inaba Y, Yamaura H, Sato Y, Kato M, Kanamoto T, Sakane M. Clinical value of CT-guided needle biopsy for retroperitoneal lesions. Korean J Radiol. 2011 May-Jun;12(3):351-7. doi: 10.3348/kjr.2011.12.3.351. Epub 2011 Apr 26. PMID: 21603294; PMCID: PMC3088852.	Wrong/no comparison as in the PICROTS
van Dalus T, van Geel AN, van Coevorden F, Hoekstra HJ, Albus-Lutter C, Slootweg PJ, Coebergh JW, Hennipman A; Dutch Soft Tissue Sarcoma Group. Soft tissue carcinoma in the retroperitoneum: an often neglected diagnosis. Eur J Surg Oncol. 2001 Feb;27(1):74-9. doi: 10.1053/ejso.2000.1057. PMID: 11247632.	Full-text unavailable.
Vanderveen KA, Thompson SM, Callstrom MR, Young WF Jr, Grant CS, Farley DR, Richards ML, Thompson GB. Biopsy of pheochromocytomas and paragangliomas: potential for disaster. Surgery. 2009 Dec;146(6):1158-66. doi: 10.1016/j.surg.2009.09.013. PMID: 19958944.	Wrong P (pheochromocytomas and paragangliomas)
Weigl H, Hohenberger P, Marx A, Vassos N, Jakob J, Galata C. Accuracy and Safety of Ultrasound-Guided Core Needle Biopsy of Soft Tissue Tumors in an Outpatient Setting: A Sarcoma Center Analysis of 392 Consecutive Patients. Cancers (Basel). 2021 Nov 12;13(22):5659. doi: 10.3390/cancers13225659. PMID: 34830814; PMCID: PMC8616355.	Wrong/no comparison as in the PICROTS
Young R, Snow H, Hendry S, Mitchell C, Slavin J, Schlicht S, Na L, Hofman MS, Gyorki DE. Correlation between percutaneous biopsy and final histopathology for retroperitoneal sarcoma: a single-centre study. ANZ J Surg. 2020 Apr;90(4):497-502. doi: 10.1111/ans.15723. Epub 2020 Feb 16. PMID: 32064728.	Wrong P (sarcoma)
Zangos S, Eichler K, Wetter A, Lehnert T, Hammerstingl R, Diebold T, Reichel P, Herzog C, Hansmann ML, Mack MG, Vogl TJ. MR-guided biopsies of lesions in the retroperitoneal space: technique and results. Eur Radiol. 2006 Feb;16(2):307-12. doi:	Wrong/no comparison as in the PICROTS

10.1007/s00330-005-2870-2. Epub 2005 Jul 30. PMID: 16059677.	

Zoekverantwoording

Algemene informatie

Richtlijn: NVvH – richtlijn bijniertumoren	
Uitgangsvraag: Wat is de plaats van biopsie in het diagnostisch traject bij patiënten met ongedefinieerde retroperitoneale massa in de bijnierloge?	
Database(s): Ovid/Medline, Embase	Datum: 5-12-2022, 8-2-2023
Periode: 2000-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: 8-2-2023 Om er zeker van te zijn dat er geen evidence wordt gemist, wordt een tweede zoekactie uitgevoerd naar algemene SR's. De resultaten zijn toegevoegd aan Rayyan. 5-12-2023 Voor deze vraag is gezocht met de volgende concepten: Retroperitoneale massa EN biopsie EN sensitiviteit, specificiteit De systematische reviews, RCTs en observationele studies worden aangeboden in Rayyan. Bij onvoldoende bewijs kan op een later moment de set: overige diagnostische studies, worden toegevoegd. De sleutelartikelen van Williams en Bancos worden niet gevonden omdat niet wordt gesproken over retroperitoneal in titel, abstract of indexterm. 1. Williams AR, Hammer GD, Else T. Transcutaneous biopsy of adrenocortical carcinoma is rarely helpful in diagnosis, potentially harmful, but does not affect patient outcome. Eur J Endocrinol. 2014 Jun;170(6):829-35. doi: 10.1530/EJE-13-1033. PMID: 24836548; PMCID: PMC4096775. 4. Bancos I, Tamhane S, Shah M, Delivanis DA, Alahdab F, Arlt W, Fassnacht M, Murad MH. DIAGNOSIS OF ENDOCRINE DISEASE: The diagnostic performance of adrenal biopsy: a systematic review and meta-analysis. Eur J Endocrinol. 2016 Aug;175(2):R65-80. doi: 10.1530/EJE-16-0297. Epub 2016 Jun 2. PMID: 27257146.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 5-12-2022 met relevante zoektermen gezocht vanaf 2000 naar systematishe reviews, RCTs en observationele studies over de plaats van biopsie in het diagnostisch traject bij patiënten met ongedefinieerde retroperitoneale massa in de bijnierloge. De literatuurzoekactie leverde 241 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld t.o.v. Rayyan 5-12-2023**

SRs	42	27	27*
RCTs			
Observationele studies			
Totaal			
5-12-2023	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs	26	12	28*
RCTs	6	2	6*
Observationele studies	151	109	207*
Overige diagnostische studies	359	235	467
Totaal			

in Rayyan

Zoekstrategie

Embase

No.	Query	Results
#16	#6 NOT #13 NOT #12 NOT #11 Overige diagnostische studies	359
#15	#13 NOT #12 NOT #11 OBS	151
#14	#12 NOT #11 RCT	6
#13	#6 AND (#9 OR #10)	165
#12	#6 AND #8	7
#11	#6 AND #7 SR	26
#10	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR (('or' OR 'rr') NEAR/6 ci):ab)))	13666234
#9	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	7384873
#8	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1989876

#7	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	881344
#6	#4 AND #5	542
#5	'sensitivity and specificity'/de OR sensitiv*:ab,ti OR specific*:ab,ti OR predict*:ab,ti OR 'roc curve':ab,ti OR 'receiver operator':ab,ti OR 'receiver operators':ab,ti OR likelihood:ab,ti OR 'diagnostic error'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'inter observer':ab,ti OR 'intra observer':ab,ti OR interobserver:ab,ti OR intraobserver:ab,ti OR validity:ab,ti OR kappa:ab,ti OR reliability:ab,ti OR reproducibility:ab,ti OR ((test NEAR/2 're-test'):ab,ti) OR ((test NEAR/2 'retest'):ab,ti) OR 'reproducibility'/exp OR accuracy:ab,ti OR 'differential diagnosis'/exp OR 'validation study'/de OR 'measurement precision'/exp OR 'diagnostic value'/exp OR 'reliability'/exp OR 'predictive value'/exp OR ppv:ti,ab,kw OR npv:ti,ab,kw	9513510
#4	#3 AND [1-1-2000]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1663
#3	#1 AND #2	2802
#2	'biopsy'/exp OR biop*:ti,ab,kw OR 'tissue sampl*':ti,ab,kw	1344606
#1	'retroperitoneal tumor'/exp OR ((atypical NEAR/3 (retroperitoneal OR adrenal)):ti,ab,kw) OR ((('adrenal fossa' OR retroperitoneal) NEAR/4 (mass* OR tumor* OR tumour* OR cancer* OR malignan*)):ti,ab,kw)	16823

Ovid/Medline

#	Searches	Results
17	11 not 14 not 13 not 12 Overige diagnostische studies	235
16	14 not 13 not 12 OBS	109
15	13 not 12 RCT	2
14	11 and (8 or 9)	117
13	11 and 7	3
12	11 and 6 SR	13
11	5 and 10	359
10	exp "Sensitivity and Specificity"/ or (Sensitiv* or Specific*).ti,ab. or (predict* or ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab. or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or Diagnosis, Differential/ or Validation Study/	7620814
9	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5302550
8	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4306694

7	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1566763
6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	633718
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1059
4	limit 3 to yr="2000 -Current"	1082
3	1 and 2	1642
2	exp Biopsy/ or (biop* or "tissue sampl*").ti,ab,kf.	782417
1	Retroperitoneal Neoplasms/ or (atypical adj3 (retroperitoneal or adrenal)).ti,ab,kf. or ((adrenal fossa or retroperitoneal) adj4 (mass* or tumor* or tumour* or cancer* or malignan*)).ti,ab,kf.	13632

Module 9 – Behandeling bijniermetastasen

Uitgangsvraag
Wat is de rol van chirurgie versus stereotactische radiotherapie voor een bijniermetastase van een primaire solide tumor elders (bijvoorbeeld longcarcinoom, melanoom, niercelcarcinoom, mammacarcinoom of colorectaal carcinoom)?

Inleiding
De bijnieren vormen een frequente locatie voor metastasering van verschillende solide tumoren en lokale behandelingen worden steeds vaker toegepast. Wanneer patiënten die zich presenteren met een solitaire bijniermetastase, of een beperkt aantal metastasen in de bijnier(en), fit zijn (bijv. goede performance status, medisch operabel) en daarnaast eveneens een bepaalde (adequate) prognose hebben, is lokale therapie van de bijnier te overwegen.
Voor beperkt progressieve of persisterende bijnier ziekte wordt een radicaal lokale behandeling steeds vaker aanbevolen, omdat er enerzijds steeds meer systemische behandelopties beschikbaar gekomen zijn met uitzicht op een langere prognose en deze anderszins niet altijd effectief zijn voor de behandeling van bijniermetastasen.
Lokale therapie voor geselecteerde kankerpatiënten met oligo-gemetastaseerde ziekte (OMD, dit omvat*: synchroon/metachroon oligo-metastasen en oligo-progressieve/persisterende ziekte*) is nu een door een richtlijn ondersteunde behandeling geworden (bijvoorbeeld door European Society for Medical Oncology (ESMO)), voor bepaalde primaire tumoren. Bijniermetastasen komen in de context van diverse primaire tumoren vaak voor en het "multidisciplinaire overleg" voor de behandeling van (o.a.) bijnier/endocriene tumoren (MDO) moet zich bewust zijn van de lokale behandelopties.
Chirurgie is de historische eerste-keuze lokale behandeling voor bijniermetastasen, maar ontwikkelingen in de radiotherapie maken stereotactische radiotherapie een reëel alternatief. Daarom richt deze module zich op de vraag: *Wat is de rol van chirurgie van een bijniermetastase van een primaire solide tumor elders?*

Search and select
A systematic review of the literature was performed to answer the following question:
What is the effect of surgery compared to (stereotactic) radiotherapy in patients with adrenal metastasis from solid tumors?

P (Patients)	patients with adrenal metastasis (e.g. from lung, melanoma, kidney, breast or colon carcinoma)
I (Intervention)	surgery
C (Control)	(stereotactic) radiotherapy
O (Outcomes)	overall survival, local control, progression-free survival, complications, mortality

Relevant outcome measures
The guideline development group considered overall survival, local control and progression-free survival as critical outcome measures for decision making; and complications and mortality as an important outcome measure for decision making.

The guideline development group defined the outcome measures as follows:

- Overall survival: Time to death from any cause
- Local control: The absence of progression in/in the region of a treated adrenal gland metastasis

- Progression-free survival: Time from randomization or initiation of treatment to the occurrence of disease progression or death from any cause
- Complications: Number of treatment-related complications <90 days
- Mortality: Death rate

The working group defined the following differences as a minimal clinically (patient) important difference:

- Overall survival: Absolute difference >5% or absolute difference >3% and Hazard Ratio (HR) <0.7
- Local control: Absolute difference >5%
- Progression-free survival: Absolute difference >5%, or absolute difference >3% and HR <0.7
- Complications: Absolute difference >5% for lethal complications, or >10% for serious complications
- Mortality: Absolute difference >5%

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2000 until 01-03-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 512 hits. Studies were selected based on the following criteria:

- Systematic reviews, randomized controlled trials, or observational comparative studies;
- Full-text English or Dutch language publication;
- Complying with the PICO criteria (directly comparing surgery with radiotherapy in patients with adrenal metastasis).

Forty-five studies were initially selected based on title and abstract screening. After reading the full text, 45 studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Results

No studies were included in the analysis of the literature.

Summary of literature

Description of studies

Not applicable.

Results

Overall survival, local control, progression-free survival, complications, mortality

No studies were found that directly compared surgery with radiotherapy in patients with adrenal metastasis on the outcomes: overall survival, local control, progression-free survival, complications, and mortality.

Level of evidence of the literature

Overall survival, local control, progression-free survival, complications, mortality

The level of evidence for the comparison surgery versus radiotherapy could not be assessed for the outcomes: overall survival, local control, progression-free survival, complications, and mortality since no appropriate studies were found.

Conclusions

Overall survival, local control, progression-free survival, complications, mortality

- **GRADE**	No studies were found on the effectiveness of metastatic adrenal surgery compared with (stereotactic) radiotherapy for the outcomes: overall survival, local control, progression-free survival, complications, and mortality in patients with adrenal metastasis from solid tumors including primary lung, melanoma, kidney, breast or colorectal carcinoma. *Source: -*

Overwegingen – van bewijs naar aanbeveling

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

Het is tot op heden onduidelijk wat de effectiviteit van een adrenalectomie is vergeleken met (stereotactische) radiotherapie als behandeling voor patiënten met bijniermetastasen van solide tumoren, want literatuuronderzoek leverde geen studies op die een directe vergelijking maakten tussen deze twee lokale behandelmodaliteiten. Rekening houdend met het gebrek aan vergelijkende data, zijn beschikbare observationele 'single arm' studies gebruikt om pragmatische/praktische aanbevelingen te doen, die tevens zijn gebaseerd op "expert-opinion".

Er werden 'single arm' studies van beide modaliteiten geïncludeerd in de review van Thomsen (2017) over geïsoleerde of oligo-gemetastaseerde bijniertumoren secundair aan niet-kleincellig longcarcinoom. In deze review werden 23 studies geïncludeerd die uitkomsten na adrenalectomie (gepubliceerd 1990-2015, 464 patiënten) en 6 studies die uitkomsten na radiotherapie (gepubliceerd 2008-2014, 57 patiënten) rapporteerden; 26/29 studies waren retrospectief. De klinische uitkomsten werden beschreven voor de geïncludeerde studies, maar er was geen meta-analyse gedaan en chirurgie werd dus niet direct vergeleken met radiotherapie in één studie. Het ruwe gemiddelde lokale recidief percentage (alhoewel niet beschreven in alle studies) was 14% na adrenalectomie en 15% na radiotherapie.

Ook zijn er recente systematische reviews beschikbaar over de afzonderlijke modaliteiten in relatie tot bijniermetastasen. Zo publiceerde Chen (2020) een gepoolde meta-analyse en een systematische review over uitkomsten van stereotactische bestraling bij bijniermetastasen (39 studies, 1006 patiënten). Lokale controle was gerelateerd aan de bestralingsdosis (93% en 86% na 1 en 2 jaar met de hoogste dosis) en er was weinig significante toxiciteit (overall graad 3+ toxiciteit 2%).
Sforza (2021) publiceerde een analyse van 477 patiënten behandeld met robotische- of laparoscopische adrenalectomie in twee centra (2008-2018) en vond dat tumorgrootte gerelateerd was aan de gemiddelde kans op complicaties.
Strong (2007) publiceerde dat bijniertumoren na laparoscopische adrenalectomie met een diameter van meer dan 4.5 cm meer kans hadden op lokaal recidief.

De retrospectieve studie van **Metman (2021)** laat zien dat er in twee grote academische centra in Nederland slechts 95 patiënten geopereerd werden over een periode van bijna 20 jaar (2001-2020). Ondanks dat deze patiënten behandeld werden in gespecialiseerde centra, komen complicaties relatief vaak voor: in deze serie had 56% patiënten een minimaal invasieve operatie (11% uiteindelijk open), was de mediane opnameduur 6.8 dagen, was de 30-dagen mortaliteit 2% en had 38% één of meer complicaties. In een serie van 43 patiënten met bijniermetastasen geopereerd tussen 2009-2019 (van Vliet, 2022) had 58% patiënten een minimaal invasieve operatie (13% uiteindelijk open), was de gemiddelde opnameduur 5 dagen, was de 30-dagen mortaliteit 2% en had 16% van de patiënten graad 1-2 complicaties.

In een ander academisch centrum in Nederland werd een serie van 51 patiënten met bijniermetastasen behandeld met stereotactische radiotherapie tussen 2016-2019 (van Vliet, 2022), werd iedereen behandeld op de polikliniek. Van deze behandelingen vond 85% met 5 fracties bestraling plaats (ongeveer 15-60 minuten/fractie afhankelijk van techniek). Dat betekent dus dat patiënten klaar waren met de behandeling in circa 1,5 week. Eenenzestig procent van de patiënten had graad 1-2 vermoeidheid/misselijkheid en de maximale toxiciteit was graad 3 misselijkheid (in één patiënt).

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Stereotactische bestraling is momenteel niet beschikbaar in elk radiotherapiecentrum (zowel academische als niet-academische), dus het kan zijn dat verwijzing naar een ander centrum noodzakelijk blijkt.

De arts en patiënt/naasten moeten samen tot een gewogen en eenduidig besluit komen.
De belangrijkste doelen van de interventie voor de patiënt en eventueel verzorger(s) zullen voor elke patiënt afzonderlijk uitgevraagd moeten worden. Doelen van de losstaande interventies of van de behandeling in totaal zullen immers afgestemd moeten worden op elkaar: zo kan het doel van de totale behandeling zijn om te overleven of om de kwaliteit van leven te verhogen. Ook kan er gekozen worden om bijniermetastasen in het geheel niet te behandelen om de kwaliteit van het resterend leven zo hoog mogelijk te houden.

Kosten (middelenbeslag)
Er zijn geen data beschikbaar om betrouwbare/verdedigbare opmerkingen te maken over het relatieve verschil in kosten van chirurgie/stereotactische bestraling (op gewone of MRI-begeleide toestellen) voor de behandeling van bijniermetastasen. In een MDO zijn kosten geen onderdeel van de beslissing om een operatie of stereotactische radiotherapie te adviseren.

Aanvaardbaarheid, haalbaarheid en implementatie
Er zijn geen data gevonden om betrouwbare opmerkingen te maken over aanvaardbaarheid, haalbaarheid en implementatie van chirurgie/stereotactische bestraling (op gewone of MRI-begeleide toestellen) voor de behandeling van bijniermetastasen. Er is geen gestructureerd onderzoek gedaan in de vorm van procesevaluatie naar de haalbaarheid van chirurgie/stereotactische bestraling, maar beide worden in Nederland reeds breed (en steeds breder) toegepast. Chirurgie en stereotactische bestralingen zijn beide complexe behandelingen die uitgevoerd moeten worden door (teams van) specialisten. De behandeling van metastasen in de bijnier van andere primaire tumoren moet worden uitgevoerd in een aantal gespecialiseerde ziekenhuizen in Nederland. Specifieke expertise is vereist, maar deze is in centra voorhanden.

Aanbevelingen
Rationale van de aanbevelingen: weging van argumenten voor en tegen de interventies
Rekening houdend met het gebrek aan vergelijkende data, stellen wij dat:

(1) De fitte, technisch operabele patiënt met een relatief kleine bijniermetastase met een grote kans voor een R0 resectie die in aanmerking komt voor radicale lokale therapie verdient goede informatie over chirurgie en stereotactische radiotherapie (‘samen beslissen’).
(2) Voor niet fitte, inoperabele patiënten heeft hoge-dosis stereotactische bestraling de voorkeur. Maar ook patiënten met hogere perioperatieve risico’s, grote afwijkingen in de bijnier, met eventueel uitbreiding in omliggende organen/structuren en met een

hogere kans voor een kortere prognose (zoals patiënten met longkanker), lijken meer in aanmerking te komen voor stereotactische bestraling dan chirurgie.

(3) Voorafgaand aan een unilaterale lokale behandeling van een bijniermetastase dient er zowel bij chirurgie en stereotactische radiotherapie goed gecontroleerd te worden in de voorgeschiedenis of de contralaterale bijnier eerder al een keer bestraald of geopereerd is (of in de buurt ervan) om te anticiperen op postoperatieve/post-radiotherapie bijnierschorsinsufficiëntie. Voorafgaand aan een bilaterale lokale behandeling (bijvoorbeeld stereotactische bestraling) is verwijzing naar, en controle door, een endocrinoloog geïndiceerd vanwege de mogelijkheid voor bijnierschorsinsufficiëntie.

(4) Patiënten met oligo-metastasen in de bijnier die in aanmerking komen voor radicale lokale therapie, moeten in Nederland toegang hebben tot een behandeling van chirurgen en radiotherapeuten met de noodzakelijke ervaring op het gebied van de behandeling van de bijnier. Dit heeft consequenties voor oncologiecentra, samenwerking tussen centra en ook voor opleiding van chirurgen en radiotherapeuten.

(5) Mochten deze lokale behandelopties niet beschikbaar zijn in het desbetreffende ziekenhuis, dan is het advies de patiënt door te verwijzen naar een bijnier expertise centrum waar deze kennis wel voor handen is. In de komende jaren wordt er een toename in ervaring verwacht bij meerdere radiotherapie afdelingen in Nederland, waardoor ook lokale controle met chirurgie en hoge-dosis stereotactische radiotherapie steeds beter vergelijkbaar lijken te worden in deze centra.

- Bespreek de voor- en nadelen van chirurgie en stereotactische radiotherapie bij fitte, technisch operabele patiënten met een relatief kleine bijniermetastase en een grote kans op een R0 resectie en die in aanmerking komen voor radicale lokale therapie en maak samen de beslissing (‘samen beslissen’).

- Geef bij voorkeur een hoge-dosis stereotactische bestraling aan niet fitte, inoperabele patiënten, of aan patiënten met hogere perioperatieve risico’s, grote afwijkingen in de bijnier, met eventueel uitbreiding in omliggende organen/structuren en met een hogere kans voor een kortere prognose.

- Verwijs patiënten met oligo-metastasen in de bijnier die in aanmerking komen voor radicale lokale therapie naar een centrum waar kennis en ervaring voorhanden is, indien deze lokale behandelopties in het eigen centrum niet beschikbaar zijn.

Literatuur

Chen WC, Baal JD, Baal U, Pai J, Gottschalk A, Boreta L, Braunstein SE, Raleigh DR. Stereotactic Body Radiation Therapy of Adrenal Metastases: A Pooled Meta-Analysis and Systematic Review of 39 Studies with 1006 Patients. Int J Radiat Oncol Biol Phys. 2020 May 1;107(1):48-61. doi: 10.1016/j.ijrobp.2020.01.017. Epub 2020 Jan 27. PMID: 32001383; PMCID: PMC8177042.

Metman MJH, Viëtor CL, Seinen AJ, Berends AMA, Hemmer PHJ, Kerstens MN, Feelders RA, Franssen GJH, van Ginhoven TM, Kruijff S. Outcomes after Surgical Treatment of Metastatic Disease in the Adrenal Gland; Valuable for the Patient? Cancers (Basel). 2021 Dec 29;14(1):156. doi: 10.3390/cancers14010156. PMID: 35008320

Sforza S, Minervini A, Tellini R, Ji C, Bergamini C, Giordano A, Lu Q, Chen W, Zhang F, Ji H, Di Maida F, Prosperi P, Masieri L, Carini M, Valeri A, Guo H. Perioperative outcomes of robotic

and laparoscopic adrenalectomy: a large international multicenter experience. Surg Endosc. 2021 Apr;35(4):1801-1807. doi: 10.1007/s00464-020-07578-5. Epub 2020 Apr 23. PMID: 32328826.

Sheikh S, Chen H, Sahgal A, Poon I, Erler D, Badellino S, Dagan R, Foote MC, Louie AV, Redmond KJ, Ricardi U, Biswas T. An analysis of a large multi-institutional database reveals important associations between treatment parameters and clinical outcomes for stereotactic body radiotherapy (SBRT) of oligometastatic colorectal cancer. Radiother Oncol. 2022 Feb;167:187-194. doi: 10.1016/j.radonc.2021.12.018. Epub 2021 Dec 22. PMID: 34952002

Strong VE, D'Angelica M, Tang L, Prete F, Gönen M, Coit D, Touijer KA, Fong Y, Brennan MF. Laparoscopic adrenalectomy for isolated adrenal metastasis. Ann Surg Oncol. 2007 Dec;14(12):3392-400. doi: 10.1245/s10434-007-9520-7. Epub 2007 Jul 31. PMID: 17665267.

Thomsen, B., & Fairchild, A. (2017). Adrenal Oligometastases Secondary to Non-small Cell Lung Cancer—What is the Optimal Treatment Approach?. *Oncol Hematol Rev*, *13*(2), 117-29.

van Vliet C, Dickhoff C, Bahce I, Engelsman AF, Hashemi SMS, Haasbeek CJA, Bruynzeel AME, Palacios MA, Becker-Commissaris A, Slotman BJ, Senan S, Schneiders FL. Treatment patterns for adrenal metastases using surgery and SABR during a 10-year period. Radiother Oncol. 2022 May;170:165-168. doi: 10.1016/j.radonc.2022.02.023. Epub 2022 Feb 24. PMID: 35219801

Bijlagen bij module Behandeling bijniermetastasen

Evidence tables
Not applicable.

Table of excluded studies

Reference	Reason for exclusion
Baydoun A, Chen H, Poon I, Badellino S, Dagan R, Erler D, Foote MC, Louie AV, Redmond KJ, Ricardi U, Sahgal A, Biswas T. Outcomes and toxicities in oligometastatic patients treated with stereotactic body radiotherapy for adrenal gland metastases: A multi-institutional retrospective study. Clin Transl Radiat Oncol. 2021 Oct 26;33:159-164. doi: 10.1016/j.ctro.2021.09.002. PMID: 35243027; PMCID: PMC8885400.	No direct comparison (only radiotherapy)
Bazhenova L, Newton P, Mason J, Bethel K, Nieva J, Kuhn P. Adrenal metastases in lung cancer: clinical implications of a mathematical model. J Thorac Oncol. 2014 Apr;9(4):442-6. doi: 10.1097/JTO.0000000000000133. PMID: 24736064; PMCID: PMC3989547.	Non-systematic review
Buergy D, Würschmidt F, Gkika E, Hörner-Rieber J, Knippen S, Gerum S, Balermpas P, Henkenberens C, Voglhuber T, Kornhuber C, Barczyk S, Röper B, Rashid A, Blanck O, Wittig A, Herold HU, Brunner TB, Klement RJ, Kahl KH, Ciernik IF, Ottinger A, Izaguirre V, Putz F, König L, Hoffmann M, Combs SE, Guckenberger M, Boda-Heggemann J. Stereotactic or conformal radiotherapy for adrenal metastases: Patient characteristics and outcomes in a multicenter analysis. Int J Cancer. 2021 Jul 15;149(2):358-370. doi: 10.1002/ijc.33546. Epub 2021 Mar 25. PMID: 33682927.	No direct comparison (only radiotherapy)
Casamassima F, Livi L, Masciullo S, Menichelli C, Masi L, Meattini I, Bonucci I, Agresti B, Simontacchi G, Doro R. Stereotactic radiotherapy for adrenal gland metastases: university of Florence experience. Int J Radiat Oncol Biol Phys. 2012 Feb 1;82(2):919-23. doi: 10.1016/j.ijrobp.2010.11.060. Epub 2011 Feb 6. PMID: 21300473.	No direct comparison (only radiotherapy)
Celik E, Semrau R, Baues C, Trommer-Nestler M, Baus W, Marnitz S. Robot-assisted Extracranial Stereotactic Radiotherapy of Adrenal Metastases in Oligometastatic Non-small Cell Lung Cancer. Anticancer Res. 2017 Sep;37(9):5285-5291. doi: 10.21873/anticanres.11954. PMID: 28870966.	No direct comparison (only radiotherapy)
Chalkidou A, Macmillan T, Grzeda MT, Peacock J, Summers J, Eddy S, Coker B, Patrick H, Powell H, Berry L, Webster G, Ostler P, Dickinson PD, Hatton MQ, Henry A, Keevil S, Hawkins MA, Slevin N, van As N.	No direct comparison (only radiotherapy)

Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study. Lancet Oncol. 2021 Jan;22(1):98-106. doi: 10.1016/S1470-2045(20)30537-4. PMID: 33387498.	
Chance WW, Nguyen QN, Mehran R, Welsh JW, Gomez DR, Balter P, Komaki R, Liao Z, Chang JY. Stereotactic ablative radiotherapy for adrenal gland metastases: Factors influencing outcomes, patterns of failure, and dosimetric thresholds for toxicity. Pract Radiat Oncol. 2017 May-Jun;7(3):e195-e203. doi: 10.1016/j.prro.2016.09.005. Epub 2016 Sep 13. PMID: 27743801.	No direct comparison (only radiotherapy)
Chen WC, Baal JD, Baal U, Pai J, Gottschalk A, Boreta L, Braunstein SE, Raleigh DR. Stereotactic Body Radiation Therapy of Adrenal Metastases: A Pooled Meta-Analysis and Systematic Review of 39 Studies with 1006 Patients. Int J Radiat Oncol Biol Phys. 2020 May 1;107(1):48-61. doi: 10.1016/j.ijrobp.2020.01.017. Epub 2020 Jan 27. PMID: 32001383; PMCID: PMC8177042.	No direct comparison (only radiotherapy)
Chen JY, Ardestani A, Tavakkoli A. Laparoscopic adrenal metastasectomy: appropriate, safe, and feasible. Surg Endosc. 2014 Mar;28(3):816-20. doi: 10.1007/s00464-013-3274-z. Epub 2013 Dec 14. PMID: 24337189.	No direct comparison (only surgery)
Cho JW, Lee YM, Sung TY, Yoon JH, Chung KW, Hong SJ. Factors related to improved clinical outcomes associated with adrenalectomy for metachronous adrenal metastases from solid primary carcinomas. Surg Oncol. 2018 Mar;27(1):18-22. doi: 10.1016/j.suronc.2017.11.003. Epub 2017 Nov 21. PMID: 29549899.	No direct comparison (only surgery)
De Ruysscher D, Wanders R, Hendriks LE, van Baardwijk A, Reymen B, Houben R, Bootsma G, Pitz C, van Eijsden L, Dingemans AC. Progression-Free Survival and Overall Survival Beyond 5 Years of NSCLC Patients With Synchronous Oligometastases Treated in a Prospective Phase II Trial (NCT 01282450). J Thorac Oncol. 2018 Dec;13(12):1958-1961. doi: 10.1016/j.jtho.2018.07.098. Epub 2018 Sep 22. PMID: 30253974.	No direct comparison (radiotherapy and surgery in all participants)
De Ruysscher D, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, Bootsma G, Pitz C, van Eijsden L, Geraedts W, Baumert BG, Lambin P. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). J Thorac Oncol. 2012 Oct;7(10):1547-55. doi: 10.1097/JTO.0b013e318262caf6. PMID: 22982655.	No direct comparison (radiotherapy and surgery in all participants)

Facondo G, Vullo G, Valeriani M, Ascolese AM, De Sanctis V, Osti MF. Stereotactic body radiation therapy (SBRT) for patients with oligometastatic/oligoprogressive adrenal metastases: Outcomes and toxicities profile in a monoinstitutional study. Cancer Treat Res Commun. 2021;29:100481. doi: 10.1016/j.ctarc.2021.100481. Epub 2021 Oct 21. PMID: 34700142.	No direct comparison (only radiotherapy)
Franzese C, Nicosia L, Facondo G, Lo Faro L, Cuccia F, Vullo G, Osti MF, Alongi F, Scorsetti M. Stereotactic body radiation therapy for adrenal gland metastases: outcome and predictive factors from a multicenter analysis. Clin Exp Metastasis. 2021 Dec;38(6):511-518. doi: 10.1007/s10585-021-10124-9. Epub 2021 Oct 15. PMID: 34651241.	No direct comparison (only radiotherapy)
Franzese C, Stefanini S, Massaro M, Comito T, Navarria P, Clerici E, Teriaca A, Franceschini D, Reggiori G, Tomatis S, Lania A, Scorsetti M. Phase II trial of stereotactic body radiation therapy on adrenal gland metastases: evaluation of efficacy and impact on hormonal production. J Cancer Res Clin Oncol. 2021 Dec;147(12):3619-3625. doi: 10.1007/s00432-021-03807-z. Epub 2021 Sep 18. PMID: 34537907.	No direct comparison (only radiotherapy)
Glenn JA, Kiernan CM, Yen TW, Solorzano CC, Carr AA, Evans DB, Wang TS. Management of suspected adrenal metastases at 2 academic medical centers. Am J Surg. 2016 Apr;211(4):664-70. doi: 10.1016/j.amjsurg.2015.11.019. Epub 2016 Jan 5. PMID: 26822269.	No direct comparison (only surgery)
Guckenberger, M., Lehmann, K., & Opitz, I. (2020). Oligometastatic non-small-cell lung cancer: local treatment options for pulmonary and adrenal metastases. ONKOLOGE, 26(9), 800-815.	No full-text available
Gunjur A, Duong C, Ball D, Siva S. Surgical and ablative therapies for the management of adrenal 'oligometastases' - A systematic review. Cancer Treat Rev. 2014 Aug;40(7):838-46. doi: 10.1016/j.ctrv.2014.04.001. Epub 2014 Apr 16. PMID: 24791623.	No comparative studies across modalities were reviewed
Huang SH, Kong QL, Chen XX, He JY, Qin J, Chen ZG. Adrenalectomy does not improve survival rates of patients with solitary adrenal metastasis from non-small cell lung cancer. Ther Clin Risk Manag. 2017 Mar 23;13:355-360. doi: 10.2147/TCRM.S130264. PMID: 28356749; PMCID: PMC5367455.	No direct comparison (only surgery)
Kanjo T, Albertini M, Weber S. Long-term disease-free survival after adrenalectomy for isolated colorectal metastases. Asian J Surg. 2006 Oct;29(4):291-3. doi: 10.1016/S1015-9584(09)60105-6. PMID: 17098665.	Wrong study design (case report)
Karagkiouzis G, Koulaxouzidis G, Tomos P, Spartalis ED, Konstantinou F, Charpidou A, Syrigos KN. Solitary	Non-systematic review

metastasectomy in non-small cell lung cancer. J BUON. 2012 Oct-Dec;17(4):712-8. PMID: 23335530.	
Krumeich LN, Roses RE, Kuo LE, Lindeman BM, Nehs MA, Tavakkoli A, Parangi S, Hodin RA, Fraker DL, James BC, Wang TS, Solórzano CC, Lubitz CC, Wachtel H. Survival After Adrenalectomy for Metastatic Lung Cancer. Ann Surg Oncol. 2022 Apr;29(4):2571-2579. doi: 10.1245/s10434-021-11192-7. Epub 2022 Jan 6. PMID: 34989938.	No direct comparison (only surgery)
Lanuti M. Surgical Management of Oligometastatic Non-Small Cell Lung Cancer. Thorac Surg Clin. 2016 Aug;26(3):287-94. doi: 10.1016/j.thorsurg.2016.04.002. PMID: 27427523.	Non-systematic review
Mercier O, Fadel E, Mussot S, Fabre D, Chataigner O, Chapelier A, Dartevelle P. Faut-il opérer les métastases surrénaliennes isolées des cancers bronchopulmonaires non à petites cellules? [Is surgery required for patients with isolated adrenal metastasis of non-small cell lung carcinoma?]. Presse Med. 2007 Dec;36(12 Pt 1):1743-52. French. doi: 10.1016/j.lpm.2007.04.042. Epub 2007 Sep 11. PMID: 17851028.	Full-text only available in French
Metman MJH, Viëtor CL, Seinen AJ, Berends AMA, Hemmer PHJ, Kerstens MN, Feelders RA, Franssen GJH, van Ginhoven TM, Kruijff S. Outcomes after Surgical Treatment of Metastatic Disease in the Adrenal Gland; Valuable for the Patient? Cancers (Basel). 2021 Dec 29;14(1):156. doi: 10.3390/cancers14010156. PMID: 35008320; PMCID: PMC8750225.	No direct comparison (only surgery)
Mourra N, Hoeffel C, Duvillard P, Guettier C, Flejou JF, Tiret E. Adrenalectomy for clinically isolated metastasis from colorectal carcinoma: report of eight cases. Dis Colon Rectum. 2008 Dec;51(12):1846-9. doi: 10.1007/s10350-008-9235-2. Epub 2008 Mar 4. PMID: 18317842.	Wrong study design (case report)
Oshiro Y, Takeda Y, Hirano S, Ito H, Aruga T. Role of radiotherapy for local control of asymptomatic adrenal metastasis from lung cancer. Am J Clin Oncol. 2011 Jun;34(3):249-53. doi: 10.1097/COC.0b013e3181dbb727. PMID: 20498589.	No direct comparison (only radiotherapy)
Palma DA, Haasbeek CJ, Rodrigues GB, Dahele M, Lock M, Yaremko B, Olson R, Liu M, Panarotto J, Griffioen GH, Gaede S, Slotman B, Senan S. Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): study protocol for a randomized phase II trial. BMC Cancer. 2012 Jul 23;12:305. doi: 10.1186/1471-2407-12-305. PMID: 22823994; PMCID: PMC3433376.	Wrong study design (study protocol)

Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, Mulroy L, Lock M, Rodrigues GB, Yaremko BP, Schellenberg D, Ahmad B, Senthi S, Swaminath A, Kopek N, Liu M, Moore K, Currie S, Schlijper R, Bauman GS, Laba J, Qu XM, Warner A, Senan S. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. J Clin Oncol. 2020 Sep 1;38(25):2830-2838. doi: 10.1200/JCO.20.00818. Epub 2020 Jun 2. PMID: 32484754; PMCID: PMC7460150.	No direct comparison (standard-of-care with or without radiotherapy)
Paunovic I, Zivaljevic V, Diklic A, Tausanovic K, Stojanic R, Sipetic S. Prognostic parameters after surgery for adrenal metastases: a single institution experience. Acta Chir Belg. 2014 May-Jun;114(3):198-202. doi: 10.1080/00015458.2014.11681008. PMID: 25102710.	No direct comparison (only surgery)
Pockaj BA, Wasif N, Dueck AC, Wigle DA, Boughey JC, Degnim AC, Gray RJ, McLaughlin SA, Northfelt DW, Sticca RP, Jakub JW, Perez EA. Metastasectomy and surgical resection of the primary tumor in patients with stage IV breast cancer: time for a second look? Ann Surg Oncol. 2010 Sep;17(9):2419-26. doi: 10.1245/s10434-010-1016-1. Epub 2010 Mar 16. PMID: 20232163; PMCID: PMC2930757.	Non-systematic review
Ramsingh J, O'Dwyer P, Watson C. Survival outcomes following adrenalectomy for isolated metastases to the adrenal gland. Eur J Surg Oncol. 2019 Apr;45(4):631-634. doi: 10.1016/j.ejso.2019.01.006. Epub 2019 Jan 4. PMID: 30638808.	No direct comparison (only surgery)
Sastry P, Tocock A, Coonar AS. Adrenalectomy for isolated metastasis from operable non-small-cell lung cancer. Interact Cardiovasc Thorac Surg. 2014 Apr;18(4):495-7. doi: 10.1093/icvts/ivt526. Epub 2013 Dec 18. PMID: 24357471; PMCID: PMC3957285.	Non-systematic review
Schmid, S., Passlick, B., Stuschke, M., & Griesinger, F. (2018). Oligometastatic disease of non-small cell lung cancer. ONKOLOGE, 24(12), 992-1002.	No full-text available
Scouarnec C, Pasquier D, Luu J, le Tinier F, Lebellec L, Rault E, Lartigau E, Mirabel X. Usefulness of Stereotactic Body Radiation Therapy for Treatment of Adrenal Gland Metastases. Front Oncol. 2019 Aug 7;9:732. doi: 10.3389/fonc.2019.00732. PMID: 31448234; PMCID: PMC6692476.	No direct comparison (only radiotherapy)
Shah MM, Isrow D, Fareed MM, Wen N, Ryu S, Ajlouni M, Siddiqui F. Single institution experience treating adrenal metastases with stereotactic body radiation therapy. J Cancer Res Ther. 2019 Mar;15(Supplement):S27-S32. doi: 10.4103/jcrt.JCRT_655_16. PMID: 30900616.	No direct comparison (only radiotherapy)
Spartalis E, Drikos I, Ioannidis A, Chrysikos D, Athanasiadis DI, Spartalis M, Avgerinos D. Metastatic	Non-systematic review

Carcinomas of the Adrenal Glands: From Diagnosis to Treatment. Anticancer Res. 2019 Jun;39(6):2699-2710. doi: 10.21873/anticanres.13395. PMID: 31177104.	
Thomsen, B., & Fairchild, A. (2017). Adrenal oligometastases secondary to nonsmall cell lung cancer-What is the optimal treatment approach. Oncol Hematol Rev, 13(2), 117-29.	Non-systematic review
Torok J, Wegner RE, Burton SA, Heron DE. Stereotactic body radiation therapy for adrenal metastases: a retrospective review of a noninvasive therapeutic strategy. Future Oncol. 2011 Jan;7(1):145-51. doi: 10.2217/fon.10.165. PMID: 21174545.	No direct comparison (only radiotherapy)
van Vliet, C., Schneiders, F., Engelsman, A., Hashemi, S., Bahce, I., Haasbeek, C., ... & Senan, S. (2021). Treatment patterns for adrenal metastases in the era of MR-guided stereotactic ablative radiotherapy. Radiotherapy and Oncology, 161, S572-S573.	Wrong article type (conference abstract)
Voglhuber T, Kessel KA, Oechsner M, Vogel MME, Gschwend JE, Combs SE. Single-institutional outcome-analysis of low-dose stereotactic body radiation therapy (SBRT) of adrenal gland metastases. BMC Cancer. 2020 Jun 8;20(1):536. doi: 10.1186/s12885-020-07030-w. PMID: 32513136; PMCID: PMC7282163.	No direct comparison (only radiotherapy)
Wachtel H, Roses RE, Kuo LE, Lindeman BM, Nehs MA, Tavakkoli A, Parangi S, Hodin RA, Fraker DL, James BC, Carr AA, Wang TS, Solórzano CC, Lubitz CC. Adrenalectomy for Secondary Malignancy: Patients, Outcomes, and Indications. Ann Surg. 2021 Dec 1;274(6):1073-1080. doi: 10.1097/SLA.0000000000003876. PMID: 32427760.	No direct comparison (only surgery)
Yaprak, G., Işik, N., Gemici, C., Demir, H., & Pekyürek, M. (2019). Stereotactic Body Radiotherapy for Adrenal Gland Metastases: Single-Center Experience. Turkish Journal of Oncology/Türk Onkoloji Dergisi, 34(4).	No direct comparison (only radiotherapy)
Zhao X, Zhu X, Fei J, Ren H, Cao Y, Ju X, Yuan Z, Zhang H. Short-term outcomes and clinical efficacy of stereotactic body radiation therapy (SBRT) in treatment of adrenal gland metastases from lung cancer. Radiat Oncol. 2018 Oct 22;13(1):205. doi: 10.1186/s13014-018-1152-5. PMID: 30348187; PMCID: PMC6196411.	No direct comparison (only radiotherapy)
Zhao X, Zhu X, Zhuang H, Guo X, Song Y, Ju X, Wang P, Yuan Z, Zhang H. Clinical efficacy of Stereotactic Body Radiation Therapy (SBRT) for adrenal gland metastases: A multi-center retrospective study from China. Sci Rep. 2020 May 12;10(1):7836. doi: 10.1038/s41598-020-64770-2. PMID: 32398700; PMCID: PMC7217854.	No direct comparison (only radiotherapy)

Literature search strategy

Algemene informatie

Richtlijn: NVvH Bijniertumoren	
Uitgangsvraag: Wat is de plaats van radiotherapie ten opzichte van chirurgie bij een bijniermetastase van een primaire solide tumor elders? (bijvoorbeeld longcarcinoom, melanoom, niercelcarcinoom, mammacarcinoom of colorectaal carcinoom)	
Database(s): Ovid/Medline, Embase	Datum: 1-3-2022
Periode: 2000-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende elementen: Bijniermetastase EN radiotherapie De vier sleutelartikelen over radiotherapie worden gevonden.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 1-3-2022 met relevante zoektermen gezocht naar systematische reviews en RCTs en observationele studies naar de plaats van radiotherapie ten opzichte van chirurgie bij een bijniermetastase . De literatuurzoekactie leverde 512 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	33	10	35
RCTs	43	6	39
Observationele studies	468	101	438
Overig			
Totaal			512

Zoekstrategie

Embase

No.	Query	Results
#18	#5 AND #17	4
#17	#14 OR #15 OR #16	490
#16	#9 AND (#12 OR #13) OBS	468
#15	#9 AND #11 RCT	43
#14	#9 AND #10 SR	33
#13	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	12899287
#12	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6920714
#11	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1877309
#10	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	801602
#9	#8 AND [1-1-2000]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1026
#8	#6 AND #7	1681

No.	Query	Results
#7	'radiotherapy'/exp OR 'stereotactic body radiation therapy'/exp OR 'sabr':ti,ab,kw OR 'sabrt':ti,ab,kw OR 'sbrt':ti,ab,kw OR 'bioradiant therapy':ti,ab,kw OR 'bucky ray':ti,ab,kw OR 'bucky therapy':ti,ab,kw OR 'radio therapy':ti,ab,kw OR 'radio treatment':ti,ab,kw OR 'radiohypophysectomy':ti,ab,kw OR 'radiotherap*':ti,ab,kw OR 'roentgen therapy':ti,ab,kw OR 'roentgen treatment':ti,ab,kw OR 'rontgen therapy':ti,ab,kw OR 'therapeutic radiology':ti,ab,kw OR 'x radiotherapy':ti,ab,kw OR 'x ray therapy':ti,ab,kw OR 'x ray treatment':ti,ab,kw OR 'x-ray therapy':ti,ab,kw OR irradiati*:ti,ab,kw OR radiati*:ti,ab,kw OR (((stereotactic* OR stereotaxic*) NEAR/4 radiat*):ti,ab,kw) OR 'robotic radio*':ti,ab,kw	1155113
#6	'adrenal gland'/exp AND 'metastasis'/exp OR 'adrenal metastasis'/exp OR ((adrenal NEAR/3 (oligometasta* OR metasta*)):ti,ab,kw)	7826
#5	#1 OR #2 OR #3 OR #4	5
#4	outcomes AND toxicities AND in AND oligometastatic AND patients AND treated AND with AND stereotactic AND body AND radiotherapy AND for AND adrenal AND gland AND metastases AND baydoun	2
#3	stereotactic AND body AND radiation AND therapy AND for AND adrenal AND gland AND metastases AND franzese AND 2021 NOT management:ti NOT phase:ti	1
#2	(stereotactic OR conformal) AND radiotherapy AND for AND adrenal AND metastases AND buergy AND 2021	1
#1	stereotactic AND body AND radiation AND therapy AND adrenal AND metastases AND a AND pooled AND 'meta analysis' AND systematic AND review AND of AND 39 AND studies AND with AND 1006 AND patients AND chen	1

Ovid/Medline

#	Searches	Results
12	5 and (8 or 9) OBS	101
11	5 and 7 RCT	6
10	5 and 6 SR	10
9	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5092813
8	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4078955
7	(exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/)	1354591
6	(meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-	549449

	synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	230
4	limit 3 to yr="2000 -Current"	231
3	1 and 2	262
2	exp Radiotherapy/ or (bioradiant therapy or bucky ray or bucky therap* or radio therap* or radio treatment or radiohypophysectomy or radiotherap* or roentgen therap* or roentgen treatment or rontgen therap* or therapeutic radiology or x radiotherapy or x ray therap* or x ray treatment or x-ray therapy or irradiati* or radiati*).ti,ab,kf. or robotic radio*.ti,ab,kf. or (sabr or sabrt or sbrt).ti,ab,kf.	762869
1	(exp Adrenal Glands/ and exp Neoplasm Metastasis/) or (adrenal adj3 (oligometasta* or metasta*)).ti,ab,kf.	2311

Module 10 – Minimaal invasieve chirurgie

Uitgangsvraag

Welke benadering bij minimaal invasieve chirurgie heeft de voorkeur voor het verwijderen van een bijniertumor?

Inleiding

In diverse internationale richtlijnen wordt minimaal invasieve chirurgie van bijniertumoren aanbevolen, maar niet nader gespecificeerd (Fassnacht, 2016; Zeiger, 2009; Lenders, 2014; Berruti 2012; Funder 2016). Daarbij wordt onvoldoende onderscheid gemaakt tussen enerzijds benigne en/of hormonaal actieve bijniertumoren en anderzijds het bijnierschorscarcinoom. Sinds 1992 is laparoscopische adrenalectomie geleidelijk de standaard geworden voor benigne en/of functionele bijniertumoren. Daarna is de retroperitoneoscopische adrenalectomie ontwikkeld. Deze operatietechniek gaat potentieel gepaard met minder postoperatieve pijn en een kortere opname- en herstelduur. Daarentegen is bij een retroperitoneoscopische adrenalectomie de chirurgische werkruimte beperkt en zijn anatomische herkenningspunten lastig te identificeren. Vanwege deze nadelen wordt een retroperitoneoscopische adrenalectomie minder uitgevoerd bij patiënten met een bijnierschorscarcinoom. Momenteel kiest de chirurg de minimaal invasieve operatietechniek vaak op basis van persoonlijke voorkeur en niet op basis van patiënt-specifieke afwegingen tussen de voor- en nadelen. Ook in de internationale richtlijnen wordt geen aandacht besteed aan de respectievelijke voor- en nadelen van een laparoscopische en retroperitoneoscopische adrenalectomie, ondanks het feit dat er gerandomiseerd onderzoek naar is gedaan. In deze module zal er gekeken worden naar welke operatietechniek de beste (patiënt gerelateerde) uitkomsten heeft.

Search and select

A systematic review of the literature was performed to answer the following question: What is the effect of the retroperitoneoscopic adrenalectomy when compared with laparoscopic (transperitoneal) adrenalectomy on time to recovery, complications, length of hospital stay, conversion to open surgery and postoperative pain in patients with an adrenal tumor?

P (Patients)	Patients with an adrenal tumor
I (Intervention)	Retroperitoneoscopic adrenalectomy
C (Control)	Laparoscopic (transperitoneal) adrenalectomy
O (Outcomes)	Time to recovery, complications, length of stay, conversion to open surgery and postoperative pain

Relevant outcome measures

The guideline development group considered time to recovery, complications and length of stay as a *critical* outcome measure for decision making, conversion to open surgery and postoperative pain as an *important* outcome measure for decision making.

The working group defined the outcome measures as follows:

- Time to recovery: Time to recover and return to work and/or exercise
- Complications: Serious complications Grade III to V according to the Clavien-dindo classification of surgical complications (Dindo, 2014)
- Length of stay: Length of hospital stay in number of days

The working group defined the following differences as a minimal clinically (patient) important difference:

- Time to recovery: > 1 week
- Complications: Absolute difference ≥1% for lethal complications, or ≥5% for serious complications
- Difference in length of hospital stay: > 1 day
- Conversion to open surgery: Absolute difference >5% or absolute difference >3% and Hazard Ratio (HR) <0.7
- Postoperative pain: Change of 10 on 100mm Visual Analogue Scale (VAS) (Myles, 2017)

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 07-04-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 219 hits. Studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICO;
- The intervention and comparison had to be as defined in the PICO;
- Outcomes had to be as defined in the PICO;
- Research type: Systematic review or randomized-controlled trial (RCT);
- Articles written in English or Dutch

27 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), one systematic review and one RCT, were included.

Results

Five RCTs from the systematic review and one RCT published after the search date of the systematic review, 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

The systematic review of **Arezzo (2018)** included five RCT's (Barczynski, 2014; Chai, 2017; Fernández-Cruz, 1996; Mohammadi-Fallah, 2013; Rubinstein, 2005). All RCT's compared the retroperitoneoscopic adrenalectomy (RPA) with the laparoscopic (transperitoneal) adrenalectomy (LTPA). The review only included RCT's with patients who were older than sixteen years and who underwent RPA or LTPA. In total, 244 patients participated in the five trials. The LRPA group consisted of 127 patients and the LTPA group consisted of 117 patients. In four RCT's only unilateral adrenalectomies were performed (Barczynski, 2014; Chai, 2017; Mohammadi-Fallah, 2013; Rubinstein, 2005). In one RCT both unilateral and bilateral adrenalectomies were performed (Fernández-Cruz, 1996). In total six patients (3%) underwent a bilateral adrenalectomy.

Barczynski (**2014**) included patients with an adrenal benign tumor up to 7 centimeters in diameter. The study population of Barczynski (2014) consisted of patients with aldosteronoma (21%), glucocorticoid adrenal adenoma (11%), pheochromocytoma (23%) and nonfunctioning tumor (45%). Chai (2017) also included patients with a unilateral benign tumor up to 7 centimeters in diameter. The study population of Chai (2017) consisted of patients with aldosteronoma (43%), Cushing syndrome (21%), pheochromocytoma (18%) and nonfunctioning tumor (18%). The study population of Fernández-Cruz (1996) consisted of patients with Cushing's syndrome, including Cushing's disease and Cushing's adenoma. The

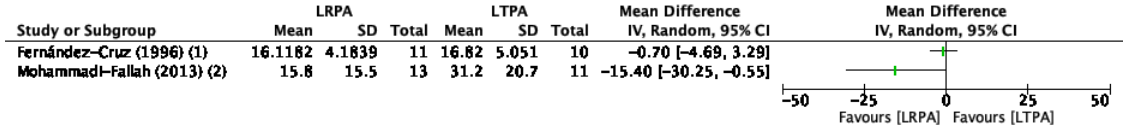
study population of Mohammadi-Fallah (2013) consisted of patients with aldosteronoma (12%), pheochromocytoma (17%), Cushing syndrome (29%) and nonfunctional tumor (42%). Mohammadi-Fallah (2013) excluded patients with a clinical suspicion of malignancy, tumors of more than six centimeters and bilateral adrenalectomy. The study population of Rubinstein (2005) consisted of patients with aldosteronoma (35%), adrenal mass (not otherwise specified) (35%), pheochromocytoma (16%), Cushing syndrome (9%), metastasis (3%) and adrenal carcinoma (2%). Rubinstein (2005) excluded patients with a bilateral adrenalectomy.
The mean age of the participants ranged from 42.2 years to 57.7 years in the RPA group and from 39.9 years to 57.0 years in the LTPA group (Arrezo, 2018).
The review of Arezzo reported the outcome times to return to normal activities, length of hospital stay and conversion to open surgery.
Data for the outcome complications were extracted from individual studies.

Kozlowski (2019) performed a single center, randomized clinical trial in Poland, comparing unilateral retroperitoneal adrenalectomy (RPA) using the posterior approach with unilateral laparoscopic transperitoneal adrenalectomy (LTPA) using the lateral approach. The adrenalectomies were performed by one surgeon with ten years of experience in laparoscopic adrenalectomies with both approaches. Patients with adrenal tumors requiring unilateral adrenalectomy and an adrenal tumor up to eight centimeters, were included. Patients with an adrenal tumor of more than eight centimeters, imaging features suggesting primary invasive malignant tumors and patients who refused to undergo randomization, were excluded. In total 77 patients were included. Patients were randomly assigned to a treatment group with no respect to remain equal group sizes. The RPA group consisted of 44 patients and the LTPA group of 33 patients. Mean age in the RPA group was 59.3 years and in the LTPA group 61.2 years. Mean Body Mass Index (BMI) in the RPA group was 29.1 kilogram per square meter (kg/m^2) and in the LTPA group 30.1 kg/m^2. In the LTPA group 4 patients (12%) and in the RPA group 9 patients (20%) had a pheochromocytoma. Cushing syndrome was diagnosed in 5 patients (15%) in the LTPA group and in 3 patients (7%) in the RPA group. Conn's disease was diagnosed in 2 patients (6%) in the LTPA group and in 4 patients (9%) in the RPA group. Nonfunctioning tumors were diagnosed in 22 patients (67%) in the LTPA group and in 28 patients (64%) in the RPA group. Median tumor size in the RPA group was 4.1 centimeters and in the LTPA group 4.0 centimeters. There were no significant differences between treatment groups at baseline.
Kozlowski (2019) reported the outcomes postoperative hospital stay, 30-day complications and postoperative pain.

Results

Time to recovery (Critical)

Three studies in the review of Arezzo (2018) reported time to return to normal activities. (Fernández-Cruz, 1996; Mohammadi-Fallah, 2013; Rubinstein, 2005). Time to return to normal activities was reported in days. Because only two studies reported estimated mean differences (Fernández-Cruz, 1996; Mohammadi-Fallah, 2013), the pooled results are not displayed (figure 1).
Fernández-Cruz (1996) reported mean number of days to return to normal activities of 16.1 in the RPA group and 18.8 days in the LTPA group. This is not clinically relevant.
Mohammadi-Fallah (2013) reported mean number of days to return to normal activities of 15.8 days in the RPA group and 31.2 days in the LTPA group. This difference is clinically relevant.



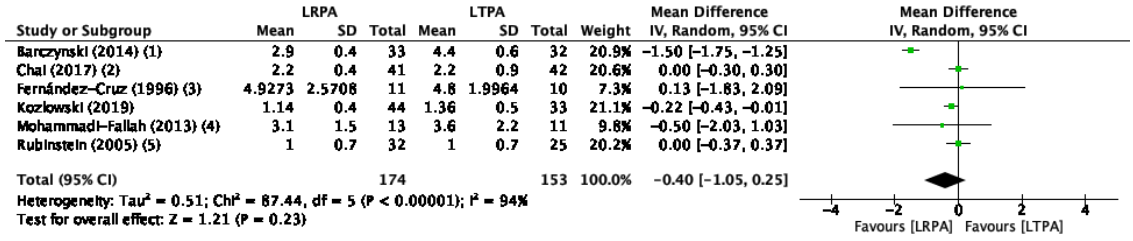
Footnotes
(1) Unilateral and bilateral adrenalectomies
(2) Unilateral adrenalectomies

Figure 4. Time to recovery with LRPA versus LTPA
CI: Confidence Interval

Rubinstein (2005) reported average convalescence of 2.3 weeks in the RPA group and 4.7 weeks in the LTPA group. This difference is clinically relevant.

Complications (Critical)
One study from the review of Arezzo (2018) (Barczynski, 2014) and the one additional study (Kozlowski, 2019) reported grade III-V complications according to the Clavien-Dindo classification.
Barczynski (2014) reported short-term postoperative complications. Barczynski (2014) reported zero grade III-V complications in the RPA group and one grade III-V complication (3.1%) in the LTPA group.
Kozlowski (2019) reported 30-day complications. Kozlowski (2019) reported zero grade III-V complications in the RPA group and zero grade III-V complications in the LTPA group.

Length of stay (Critical)
Length of stay was reported in five studies in the review of Arezzo (2018) (Barczynski, 2014; Chai, 2017; Fernández-Cruz, 1996; Mohammadi-Fallah, 2013; Rubinstein, 2005) and the one additional study (Kozlowski, 2019). The pooled mean difference (MD) was -0.40 (95%CI -1.05 to 0.25) favoring retroperitoneal adrenalectomy (figure 2). This difference is not clinically relevant.



Footnotes
(1) Unilateral adrenalectomies
(2) Unilateral adrenalectomies
(3) Unilateral and bilateral adrenalectomies
(4) Unilateral adrenalectomies
(5) Unilateral adrenalectomies

Figure 2. Length of stay with RPA versus LTPA
Z: p-value of pooled effect; df: degrees of freedom, I^2: statistical heterogeneity, CI: confidence interval

Conversion to open surgery (Important)
Conversion to open surgery was reported in four studies in the review of **Arezzo (2018)** (Barczynski, 2014; Chai, 2017; Mohammadi-Fallah, 2013; Rubinstein, 2005) (figure 3). In the study of Barczynski (2014), no events of conversion to open surgery occurred, therefore Risk Ratio (RR) was not estimable.
The pooled RR was 1.72 (95%CI 0.31 to 9.62) favoring transperitoneal adrenalectomy. This difference is clinically relevant.

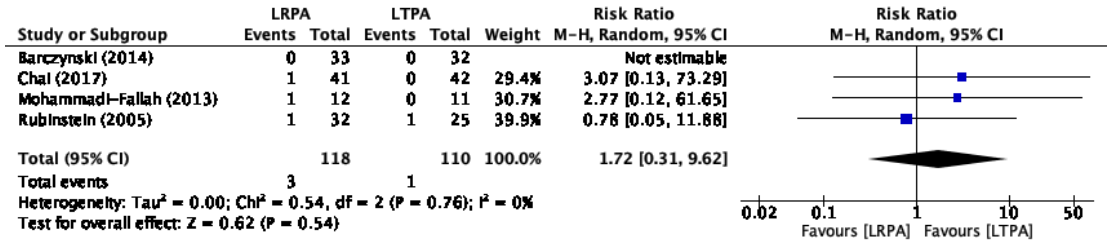


Figure 3. Proportion of conversion to open surgery events with RPA versus LTPA
Z: p-value of pooled effect; df: degrees of freedom, I^2: statistical heterogeneity, CI: confidence interval

Postoperative pain (important)
One study reported postoperative pain at day 1 (Kozlowski, 2019) using the Visual Analog Scale (VAS) ranging from 0 for no pain to 10 for maximal pain.
Kozlowski (2019) reported mean VAS score of 3.4 (SD 1) in the LRPA group and 4.2 (SD 1) in the LTPA group. This difference is not clinically relevant.

Level of evidence of the literature
Time to recovery
The level of evidence regarding the outcome measure **time to recovery** was downgraded by three levels because of study limitations (-1; risk of bias because of unclear risk for selection and performance bias), conflicting results (-1; inconsistency because of methodological heterogeneity) and number of included patients (-1; imprecision because of low sample size). The level of evidence was therefore graded as very low.

Complications
The level of evidence regarding the outcome measure **complications** was downgraded by three levels because of study limitations (-1; risk of bias because of selection, performance and detection bias) and number of included patients (-2; imprecision because of low sample size, small number of events and the confidence intervals including the possibility of a positive effect, no effect or a negative effect). The level of evidence was therefore graded as very low.

Length of stay
The level of evidence regarding the outcome measure **length of stay** was downgraded by two levels because of study limitations (-1; risk of bias because of selection, performance and detection bias) and number of included patients (-1; imprecision because of low sample size and the confidence intervals including the possibility of a positive effect or no effect). The level of evidence was therefore graded as low.

Conversion to open surgery
The level of evidence regarding the outcome measure **conversion to open surgery** was downgraded by three levels because of study limitations (-1; risk of bias because of unclear risk of selection bias), conflicting results (-1; inconsistency because of methodological heterogeneity) and number of included patients (-1; imprecision because of low sample size, small number of events and the confidence intervals including the possibility of a positive effect, no effect or a negative effect). The level of evidence was therefore graded as very low.

Postoperative pain
The level of evidence regarding the outcome measure **postoperative pain** was downgraded by three levels because of study limitations (-1; risk of bias because of selection bias, selective reporting and lack of blinding) and number of included patients (-2; imprecision because of single study and low sample size). The level of evidence was therefore graded as very low.

Conclusions

Time to recovery

Very low GRADE	The evidence is very uncertain about the effect of retroperitoneoscopic adrenalectomy on time to recovery when compared with laparoscopic transperitoneal adrenalectomy in patients with an adrenal tumor. *Source: Arezzo, 2018*

Complications

Very low GRADE	The evidence is very uncertain about the effect of retroperitoneoscopic adrenalectomy on complications when compared with laparoscopic transperitoneal adrenalectomy in patients with an adrenal tumor. *Source: Arezzo, 2018; Kozlowski, 2019*

Length of stay

Low GRADE	The evidence suggests that retroperitoneoscopic adrenalectomy results in little to no difference in length of stay when compared with transperitoneal adrenalectomy in patients with an adrenal tumor. *Source: Arezzo, 2018; Kozlowski, 2019*

Conversion to open surgery

Very low GRADE	The evidence is very uncertain about the effect of retroperitoneoscopic adrenalectomy on conversion to open surgery when compared with laparoscopic transperitoneal adrenalectomy in patients with an adrenal tumor. *Source: Arezzo, 2018*

Postoperative pain

Very low GRADE	The evidence is very uncertain about the effect of retroperitoneoscopic adrenalectomy on postoperative pain when compared with laparoscopic transperitoneal adrenalectomy in patients with an adrenal tumor. *Source: Kozlowski, 2019*

Overwegingen – van bewijs naar aanbeveling

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

Voor de drie cruciale uitkomstmaten (tijd tot herstel, complicaties en opnameduur) werden resultaten gerapporteerd.

Drie studies rapporteerden tijd tot herstel (Fernández-Cruz, 1996; Mohammadi-Fallah, 2013; Rubinstein, 2005). Twee studies (Mohammadi-Fallah, 2013; Rubinstein, 2005) rapporteerden een klinisch relevant verschil van meer dan één week in het voordeel van de retroperitoneale benadering echter doorkruist het 95% betrouwbaarheidsinterval de grens van klinische besluitvorming waardoor het ware effect mogelijk ook niet klinisch relevant kan zijn. Eén studie rapporteerde geen klinisch relevant verschil tussen beide benaderingen (Fernández-Cruz, 1996). De studies gebruikten verschillende definities voor de uitkomsten en er waren verschillen tussen de studie populaties. Eén studie had alleen patiënten met het syndroom van Cushing geïncludeerd en twee studies hebben patiënten met zowel benigne als maligne bijniertumoren geïncludeerd.

Twee studies (Barczynski, 2014; Kozlowski, 2019) rapporteerden graad III-V complicaties (volgens de Clavien-Dindo classificatie) waarbij twee studies korte termijn complicaties rapporteerden waarbij geen klinisch relevante verschillen zijn gevonden tussen de retroperitoneale benadering en transperitoneale benadering.
Vijf studies rapporteerden opnameduur (Barczynski, 2014; Chai, 2017; Fernández-Cruz, 1996; Mohammadi-Fallah, 2013; Rubinstein, 2005; Kozlowski, 2019). Er was geen klinisch relevant verschil tussen de verschillende behandelingen. Een zeer recent internationaal, retrospectief observationeel onderzoek laat wel een kortere opnameduur zien voor patiënten die een retroperitoneale benadering ondergingen (Van den Heede, 2023).

De bewijskracht van twee (tijd tot herstel en complicaties) van de drie cruciale uitkomstmaten is zeer laag. Er was sprake van risico op bias door het onduidelijk beschrijven van de selectie van participanten, gebrek aan blindering en onduidelijkheid over de rapportage van uitkomsten. Er was sprake van inconsistentie tussen de studies vanwege verschillende studie populaties. Naast de gemiddelde leeftijd die verschilde tussen de studies, hebben de onderzoekers, patiënten geïncludeerd met verschillende bijniertumoren of bijnier adenomen of alleen patiënten met het syndroom van Cushing. Daarnaast zijn er kleine patiëntaantallen gebruikt waarop de resultaten gebaseerd zijn.

Het is lastig om een conclusie te trekken. De gerapporteerde resultaten in twee studies (Mohammadi-Fallah, 2013; Rubinstein, 2005) voor de uitkomstmaat tijd tot herstel lijken een mogelijk klinisch relevant voordeel te geven voor de retroperitoneale benadering maar de bewijskracht is zeer onzeker. Eén studie rapporteerde postoperatieve pijn (Kozlowski, 2019) waarbij er een verschil gevonden was in het voordeel van de retroperitoneale benadering maar dit verschil niet klinisch relevant was. Met betrekking tot de belangrijke uitkomstmaat conversie naar open chirurgie is er een klinisch relevant verschil in het voordeel van de transperitoneale benadering.
Ook de bewijskracht voor deze uitkomstmaten is zeer laag door het risico op bias, heterogeniteit tussen de studies en het kleine patiëntaantal waarop de resultaten gebaseerd zijn.

Er is een aantal overwegingen dat mee kan spelen bij het maken van een keuze tussen de retroperitoneale benadering en transperitoneale behandeling. De retroperitoneale benadering is te overwegen bij patiënten met een tumor ≤7 cm en Body Mass Index (BMI) <35 met oog op het (geringe) voordeel in herstelduur van de patiënt. Tumor grootte van ≤7 cm is ook als inclusiecriterium gehanteerd door Barczynski (2014). In de studie van Barczynski (2014) hadden slecht 15 van de 65 patiënten een BMI >30. De nadelen van buikligging (zoals beademingsvoorwaarden, veneuze return en beperkte chirurgische werkruimte) gaan zwaarder wegen bij hoge BMI en langdurige operatieduur (complexe/grote tumoren). De consensus onder de werkgroepleden is dat dit bij BMI ≥35 een rol speelt.
Overweeg retroperitoneale benadering na eerdere peritonitis of transperitoneale chirurgie vanwege potentiële inwendige verlittekening die via deze route wordt vermeden.
Als beide bijnieren verwijderd moeten worden heeft de posterieure retroperitoneale benadering voordeel voor operatieduur (van Uitert, 2017). Bij verhoogde kans op littekenbreuk, zoals door wondgenezingsstoornis bij diabetes mellitus, is een overweging om retroperitoneaal te opereren waarbij dit nagenoeg niet voorkomt.
Overweeg de transperitoneale benadering bij grotere tumoren en bij primair maligne tumoren zoals een adrenocorticaal carcinoom (ACC) in verband met werkruimte en kans op tumor spill. Houdt daarbij voor ogen dat open chirurgie nog steeds de gouden standaard is bij (grote) ACCs. Ook na eerdere retroperitoneale chirurgie kan de transperitoneale benadering uitkomst bieden in verband met verlittekening van het operatiegebied.

De voorkeur en ervaring van de operateur speelt een rol bij keuze voor chirurgische benadering, waarbij factoren als toenemende centralisatie, volume, leercurve en expertise met (verschillende) technieken doorslaggevend zijn (van Uitert, 2017).

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Bespreek de voorkeur van de patiënt met inachtneming van factoren als (mogelijk voordeel in) herstelduur en terugkeer naar werk, kans op littekenbreuk en postoperatieve pijn die volgens de werkgroep minder is na retroperitoneale benadering.

Kosten (middelenbeslag)
Er wordt verwacht dat de retroperitoneale benadering efficiënter is, door een kortere operatieduur en mogelijk kortere hersteltijd, met minder kosten. Hiervoor dient de operateur de leercurve te hebben doorlopen met optimale voorbereiding van het operatieteam op de specifieke aspecten van de techniek. Het gebruik van materialen en apparatuur is vergelijkbaar tussen beide technieken. Echter, dit is niet gebaseerd op wetenschappelijke (kosteneffectiviteit) studies.

Aanvaardbaarheid, haalbaarheid en implementatie
De werkgroep is van mening dat bijnierchirurgie in centra moet plaatsvinden waar voldoende exposure van patiënten bestaat en ervaring met verschillende operatietechnieken beschikbaar is. Training van deze operatietechnieken is van belang voor optimale veiligheid van de patiënt en een korte leercurve van bijnierchirurgen. Het opzetten van een programma waarin gebruik wordt gemaakt van het proctoring principe door een (inter)nationale expert kan de training optimaliseren. Hiervoor zijn voldoende ervaren bijnierchirurgen en operatieteams in Nederland, maar ook in sommige omringende landen beschikbaar.

Aanbeveling(en)
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Er lijkt, op basis van de cruciale uitkomstmaten (tijd tot herstel, complicaties en opnameduur) mogelijk een licht voordeel te zijn voor de retroperitoneale benadering. Met betrekking tot de belangrijke uitkomstmaat conversie naar open chirurgie is er een klinisch relevant verschil in het voordeel van de transperitoneale benadering die kan zijn gerelateerd aan de werkruimte bij deze benadering.

De bewijskracht van twee van de drie cruciale uitkomstmaten is zeer laag door risico op bias en inconsistentie vanwege verschillende patiënten populaties. Ook de bewijskracht voor conversie is zeer laag door het risico op bias, heterogeniteit tussen de studies en het kleine patiëntaantal waarop de resultaten gebaseerd zijn.

Overweeg retroperitoneoscopische benadering bij de volgende patiënten:
- Met een tumor ≤7 cm en BMI <35
- Na eerdere peritonitis en transperitoneale chirurgie
- Met indicatie om beiderzijds de bijnier te verwijderen

Overweeg de laparoscopische transperitoneale benadering bij de volgende patiënten:
- Bij patiënten met grotere en/of primair maligne tumoren (ACC) in verband met chirurgische werkruimte. Weeg hierbij altijd af of een minimaal invasieve benadering de voorkeur heeft en oncologisch veilig is
- Bij patiënten met een hoge BMI (≥35) of na eerdere retroperitoneale chirurgie

Spoedconversie van retroperitoneoscopische benadering (in buikligging) naar laparoscopische of open benadering is complex, vanwege de tijd die het kost om de positie van de patiënt aan te passen naar zij- of rugligging.

Voorkeur van de patiënt, de voor- en nadelen per operatietechniek en de ervaring van de chirurg met verschillende technieken zijn uiteindelijk doorslaggevend in het preoperatieve gesprek met de patiënt en de keuze voor operatietechniek.

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Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D, Fishman E, Kharlip J; American Association of Clinical Endocrinologists; American Association of Endocrine Surgeons. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocr Pract. 2009 Jul-Aug;15 Suppl 1:1-20. doi: 10.4158/EP.15.S1.1. PMID: 19632967.

Bijlagen bij module Minimaal invasieve chirurgie

Evidence tables

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

Research question: What is the effect of the retroperitoneoscopic adrenalectomy when compared to laparoscopic adrenalectomy on time to recovery, complications, duration of hospital stay and conversion in patients with an adrenal tumor?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Arezzo, 2018 Study characteristics and results are extracted from the SR unless stated otherwise	SR and meta-analysis of RCTs *Literature search up to April 2018* **A**: Barczynski, 2014 **B**: Chai, 2017 **C**: Fernández-Cruz, 1996 **D**: Mohammadi-Fallah, 2013 **E**: Rubinstein, 2005 <u>Study design</u>: **A**: Parallel RCT **B**: Parallel RCT **C**: Parallel RCT **D**: Parallel RCT **E**: Parallel RCT <u>Setting and Country</u>:	Inclusion criteria SR: - Randomized Controlled Trials - Data from adults (> 16 years) - Patients who underwent laparoscopic transperitoneal or laparoscopic retroperitoneal adrenalectomy for preoperatively assessed adrenal tumors Exclusion criteria SR: No exclusion for systematic review were reported.	Describe intervention: **A**: Retroperitoneal adrenalectomy **B**: Retroperitoneal adrenalectomy **C**: Retroperitoneal adrenalectomy **D**: Retroperitoneal adrenalectomy **E**: Retroperitoneal adrenalectomy	Describe control: **A**: Transperitoneal adrenalectomy **B**: Transperitoneal adrenalectomy **C**: Transperitoneal adrenalectomy **D**: Transperitoneal adrenalectomy **E**: Transperitoneal adrenalectomy	<u>End-point of follow-up</u>: **A**: 60 months after surgery **B**: 31.3 months **C**: Mean follow-up 9.2 months **D**: Mean follow-up 9 months **E**: Mean follow-up 5.9 years <u>For how many participants were no complete outcome data available?</u> **A:** N=5 (8%) **B**: N=0 (0%) **C**: N=0 (0%) **D**: N=0 (0%) **E**: N=0 (0%)	<u>Outcome measure-1: Time to recovery</u> Defined as: Time to return to normal activities (in days) Effect measure: Mean difference [95% CI]: **A**: Not reported **B**: Not reported **C:** -0.70 (-4.69-3.29) **D:** -15.4 (-30.25- -0.55) **E:** Not estimable Pooled effect (random effects model): -1.33 [95% CI -5.43 to 2.76] favoring retroperitoneal adrenalectomy Heterogeneity (I^2): 71% <u>Outcome measure-2: Complications[a]</u> Defined as: Postoperative complications (grade I-V)	<u>Facultative</u>: *Author's conclusion:* The body of evidence on laparoscopic retroperitoneal adrenalectomy compared with laparoscopic transperitoneal adrenalectomy is limited. Very low-quality evidence indicates that for relatively small lesions (less than 6 cm to 7 cm), late morbidity might be reduced following the retroperitoneal approach. While no conclusive differences were observed between intervention and comparator groups in the analysis of operative parameters, the analysis of some post-operative parameters, such as the time to oral fluid of food intake and the time to

	A: Poland **B**: South Korea **C**: Spain **D**: Iran **E**: USA <u>Source of funding and conflicts of interest:</u> **A**: Not declared **B**: Not reported **C**: Not declared **D**: Urmia University of Medical Sciences **E**: Not declared	Main exclusion criteria reported in studies: - History of major abdominal surgery - planned bilateral adrenal surgery - Adrenal tumor larger than six centimeters of seven centimeters in diameter - Age less than 16 years or 18 years *5 studies were included* <u>Important patient characteristics at baseline</u>: <u>N, mean age in years (SD)</u> **A**: I: 76, 47.9 C: 72, 46.6 **B**: I: 63, 46.4 (11.0) C: 67, 48.0 (11.4) **C**: I: 73, 49.9 (17.8) C: 71. 39.9 (18.4) **D:** I: 62, 42.2 (median) C: 55, 42.9 (median)				Effect measure: Risk Ratio [95% CI]: **A**: 0.58 (0.24-1.41) **E:** 2.56 (0.25-26.65) Pooled effect (random effects model): 0.81 [95% CI 0.24 to 2.75] favoring retroperitoneal adrenalectomy Heterogeneity (I^2): 26% <u>Outcome measure-3: Length of hospital stay (in days)</u> Effect measure: Mean difference [95% CI]: **A**: -1.5 (-1.75- -1.25) **B**: 0 (-0.3-0.3) **C:** 0.13 (-3.11.83-2.09) **D:** -0.50 (-2.03-1.03) **E:** 0 (-0.37-0.37) Pooled effect (random effects model): -0.43 [95% CI -1.32 to 0.46] favoring retroperitoneal adrenalectomy Heterogeneity (I^2): 95% <u>Outcome measure-4: Conversion to open surgery</u> Effect measure: Risk ratio [95% CI]: **A**: Not estimable **B**: 3.07 (0.13-73.29) **C:** Not reported **D;** 2.77 (0.12-61.65) **E:** 0.78 (0.05-11.88) Pooled effect (random effects model):	ambulation, may show an advantage for the laparoscopic retroperitoneal adrenalectomy technique. Level of evidence: *Outcome time to return to normal activities:* GRADE very low because of unclear risk of performance and detection bias and because of (serious) imprecision. *Outcome length of hospital stay:* GRADE very low because of unclear risk of performance and detection bias and because of (serious) imprecision. Sensitivity analyses: There were too few trials to carry out these analyses. Clinical heterogeneity: All studies only performed unilateral adrenalectomies apart from Fernández-Cruz (1996) who performed unilateral and bilateral adrenalectomies. Rubinstein (2005) performed lateral retroperitoneal approach and not the posterior retroperitoneal approach.

		E: I: 59, 57.5 (median) C: 48, 57 (median) *<u>Body Mass Index, mean kg/m ^{2} (SD):</u>* **A**: I: 27.6 C: 27.3 **B**: I: 23.6 (3.0) C: 24.2 (3.3) **C**: NR **D:** I: 27.5 (median) C: 26.7 (median) **E:** I: 30.4 (median) C: 29.1 (median) <u>Tumor size, mean in millimeters (SD):</u> **A**: I: 39 (95%CI 10-70) C: 40 (95%CI 10-65) **B**: I: 30 (13) C: 29 (14) **C**: NR **D**: I: 26 (median) (IQR 20-50) C: 29 (median) (IQR 20-50) **E**: I: 26 (median) (IQR 17-49)				1.72 [95% CI 0.31 to 9.62] favoring transperitoneal adrenalectomy Heterogeneity (I^2): 0%	

		C: 27 (median (IQR 16-42) Groups are not comparable at baseline					
Kozlowski, 2019	Type of study: Randomized controlled trial Setting and country: Single center, Poland, between February 2015 and June 2018 Funding and conflicts of interest: The authors declare no conflict of interest	Inclusion criteria: - Patients with adrenal tumors requiring adrenalectomy - Unilateral adrenalectomy - Adrenal tumor up to 8 centimeters Exclusion criteria: - Adrenal tumors of more than 8 centimeters - Imaging features suggesting primary invasive malignant tumors - Refusal of the patients to undergo randomization N total at baseline: Intervention: 44 Control: 33 Important prognostic factors[2]: *Mean age in years (SD):* *I: 59.3 (10.2)*	Describe intervention: Unilateral laparoscopic total adrenalectomy using the posterior retroperitoneal approach (PRA) performed by one surgeon with 10 years of experience in laparoscopic adrenalectomies with both approaches.	Describe control: Unilateral laparoscopic total adrenalectomy using the lateral transperitoneal approach (LTA) performed by one surgeon with 10 years of experience in laparoscopic adrenalectomies with both approaches.	Length of follow-up: I: 28 months (SD 12) C: 28 months (SD 13) Loss-to-follow-up: Intervention: N=1 (2.3%) Reasons: Not reported Control: N =0 (0%) Incomplete outcome data: Intervention: N N=0 (0%) Control: N=1 (3%) Reasons: Death	Outcome measures and effect size (include 95%CI and p-value if available): Mean postoperative hospital stay in days (SD): I: 1.14 (0.4) C: 1.36 (0.5) MD -0.22 (95%CI -0.43- -0.01) 30-day complications (according to Dindo): I: N=4 (9%) C: N=4 (12%) RR 0.75 (95%CI 0.20-2.78)	*Authors conclusion:* The present study comparing LTA and PRA laparoscopic adrenalectomies confirmed the safety, efficacy, and very low morbidity of both techniques. The PRA proved superior to LTA in terms of lower intensity of postoperative pain and shorter hospital stay. This study only performed unilateral laparoscopic adrenalectomy.

		C: 61.2 (8.3) *Sex, male:* *I: N=21 (48%)* *C: N=13 (39%)* *Mean Body Mass Index in kg/m^2 (SD):* *I: 29.1 (5.2)* *C: 30.1 (6)* *Median tumor size in centimeters (IQR):* *I: 4.1 (1.5-7.5)* *C: 4.0 (0.8-7.5)* *No significant differences between treatment groups at baseline*					
[a] Results extracted from individual studies							

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

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

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/not applicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Arezzo, 2018	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	No

1. Research question (PICO) and inclusion criteria should be appropriate and predefined
2. Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched
3. Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons
4. Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported
5. Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)
6. Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)

7. Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I^2)?
8. An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
9. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.

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

Research question: What is the effect of the retroperitoneoscopic adrenalectomy when compared to laparoscopic adrenalectomy on time to recovery, complications, duration of hospital stay and conversion in patients with an adrenal tumor?

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Kozlowski, 2019	No information Reason: Study stated: 'To avoid any	No information	Definitely no Reason: Patients, health care providers,	Probably yes Reason: Loss to follow-up was	No information Reason: No trial registry or protocol available	No information	**HIGH (no information regarding allocation generation and concealment, no**

	disturbance of free randomization, we did not use the computer option to balance the number of patients'	Reason: No exact information on allocation concealment	outcome assessors or data analysts were not blinded	infrequent in intervention and control group. Only one patient was lost to follow-up.			**blinding and no information regarding selective outcome reporting)**

Randomization: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
Allocation concealment: refers to the protection (blinding) of the randomization process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomization (performed at a site remote from trial location). Inadequate procedures are all procedures based on inadequate randomization procedures or open allocation schedules..
Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments, but this should not affect the risk of bias judgement. Blinding of those assessing and collecting outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment or data collection (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is usually not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary. Finally, data analysts should be blinded to patient assignment to prevents that knowledge of patient assignment influences data analysis.
Lost to follow-up: If the percentage of patients lost to follow-up or the percentage of missing outcome data is large, or differs between treatment groups, or the reasons for loss to follow-up or missing outcome data differ between treatment groups, bias is likely unless the proportion of missing outcomes compared with observed event risk is not enough to have an important impact on the intervention effect estimate or appropriate imputation methods have been used.
Selective outcome reporting: Results of all predefined outcome measures should be reported; if the protocol is available (in publication or trial registry), then outcomes in the protocol and published report can be compared; if not, outcomes listed in the methods section of an article can be compared with those whose results are reported.
Other biases: Problems may include: a potential source of bias related to the specific study design used (e.g. lead-time bias or survivor bias); trial stopped early due to some data-dependent process (including formal stopping rules); relevant baseline imbalance between intervention groups; claims of fraudulent behavior; deviations from intention-to-treat (ITT) analysis; (the role of the) funding body. Note: The principles of an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.
Overall judgement of risk of bias per study and per outcome measure, including predicted direction of bias (e.g. favors experimental, or favors comparator). Note: the decision to downgrade the certainty of the evidence for a particular outcome measure is taken based on the body of evidence, i.e. considering potential bias and its impact on the certainty of the evidence in all included studies reporting on the outcome.

Table of excluded studies

Reference	Reason for exclusion
Gavriilidis P, Camenzuli C, Paspala A, Di Marco AN, Palazzo FF. Posterior Retroperitoneoscopic Versus Laparoscopic Transperitoneal Adrenalectomy: A Systematic Review by an Updated Meta-Analysis. World J Surg. 2021 Jan;45(1):168-179. doi: 10.1007/s00268-020-05759-w. Epub 2020 Aug 27. PMID: 32856097.	Wrong study design: The systematic review also includes observational studies
Meng C, Du C, Peng L, Li J, Li J, Li Y, Wu J. Comparison of Posterior Retroperitoneoscopic Adrenalectomy Versus Lateral Transperitoneal Laparoscopic Adrenalectomy for Adrenal Tumors: A Systematic Review and Meta-Analysis. Front Oncol. 2021 May 10;11:667985. doi: 10.3389/fonc.2021.667985. PMID: 34041031; PMCID: PMC8142855.	Wrong study design: The systematic review also includes observational studies
Jiang YL, Qian LJ, Li Z, Wang KE, Zhou XL, Zhou J, Ye CH. Comparison of the retroperitoneal versus Transperitoneal laparoscopic Adrenalectomy perioperative outcomes and safety for Pheochromocytoma: a meta-analysis. BMC Surg. 2020 Jan 13;20(1):12. doi: 10.1186/s12893-020-0676-4. PMID: 31931809; PMCID: PMC6958587.	Wrong population: Review only included patients with pheochromocytoma
Kwak J, Lee KE. Minimally Invasive Adrenal Surgery. Endocrinol Metab (Seoul). 2020 Dec;35(4):774-783. doi: 10.3803/EnM.2020.404. Epub 2020 Dec 23. PMID: 33397038; PMCID: PMC7803606.	Wrong design: Narrative review
Li J, Wang Y, Chang X, Han Z. Laparoscopic adrenalectomy (LA) vs open adrenalectomy (OA) for pheochromocytoma (PHEO): A systematic review and meta-analysis. Eur J Surg Oncol. 2020 Jun;46(6):991-998. doi: 10.1016/j.ejso.2020.02.009. Epub 2020 Feb 17. PMID: 32102743.	Wrong intervention versus control: Laparoscopic versus open adrenalectomy
Portelli, M., Camenzuli, C., Gafa', A. et al. Retroperitoneal vs. transperitoneal laparoscopic adrenalectomy: a meta-analysis of the literature. Eur Surg 50, 278–284 (2018)	Systematic review only included three studies: Included review of Arezzo (2018) included five.
Ball MW, Hemal AK, Allaf ME. International Consultation on Urological Diseases and European Association of Urology International Consultation on Minimally Invasive Surgery in Urology: laparoscopic and robotic adrenalectomy. BJU Int. 2017 Jan;119(1):13-21. doi: 10.1111/bju.13592. Epub 2016 Aug 19. PMID: 27431446.	Wrong intervention versus control: Laparoscopic versus robotic adrenalectomy
Gaujoux S, Mihai R; joint working group of ESES and ENSAT. European Society of Endocrine Surgeons (ESES) and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the surgical management of adrenocortical carcinoma. Br J Surg. 2017 Mar;104(4):358-376. doi: 10.1002/bjs.10414. PMID: 28199015.	Wrong design: International guideline

Conzo G, Tartaglia E, Gambardella C, Esposito D, Sciascia V, Mauriello C, Nunziata A, Siciliano G, Izzo G, Cavallo F, Thomas G, Musella M, Santini L. Minimally invasive approach for adrenal lesions: Systematic review of laparoscopic versus retroperitoneoscopic adrenalectomy and assessment of risk factors for complications. Int J Surg. 2016 Apr;28 Suppl 1:S118-23. doi: 10.1016/j.ijsu.2015.12.042. Epub 2015 Dec 18. PMID: 26708860.	Wrong design: No systematic review
Chai YJ, Kwon H, Yu HW, Kim SJ, Choi JY, Lee KE, Youn YK. Systematic Review of Surgical Approaches for Adrenal Tumors: Lateral Transperitoneal versus Posterior Retroperitoneal and Laparoscopic versus Robotic Adrenalectomy. Int J Endocrinol. 2014;2014:918346. doi: 10.1155/2014/918346. Epub 2014 Dec 17. PMID: 25587275; PMCID: PMC4281398.	Wrong study design: The systematic review only includes observational studies
Chen W, Li F, Chen D, Zhu Y, He C, Du Y, Tan W. Retroperitoneal versus transperitoneal laparoscopic adrenalectomy in adrenal tumor: a meta-analysis. Surg Laparosc Endosc Percutan Tech. 2013 Apr;23(2):121-7. doi: 10.1097/SLE.0b013e3182827b57. PMID: 23579504.	Wrong study design: The systematic review only includes observational studies
Nigri G, Rosman AS, Petrucciani N, Fancellu A, Pisano M, Zorcolo L, Ramacciato G, Melis M. Meta-analysis of trials comparing laparoscopic transperitoneal and retroperitoneal adrenalectomy. Surgery. 2013 Jan;153(1):111-9. doi: 10.1016/j.surg.2012.05.042. Epub 2012 Aug 30. PMID: 22939744.	Wrong study design: The systematic review also includes observational studies
Al-Zahrani HM. Laparoscopic adrenalectomy: An update. Arab J Urol. 2012 Mar;10(1):56-65. doi: 10.1016/j.aju.2011.11.003. Epub 2012 Jan 31. PMID: 26558005; PMCID: PMC4442880.	Wrong design: Narrative review
Constantinides VA, Christakis I, Touska P, Palazzo FF. Systematic review and meta-analysis of retroperitoneoscopic versus laparoscopic adrenalectomy. Br J Surg. 2012 Dec;99(12):1639-48. doi: 10.1002/bjs.8921. Epub 2012 Sep 28. PMID: 23023976.	Wrong study design: The systematic review also includes observational studies
Heloury Y, Muthucumaru M, Panabokke G, Cheng W, Kimber C, Leclair MD. Minimally invasive adrenalectomy in children. J Pediatr Surg. 2012 Feb;47(2):415-21. doi: 10.1016/j.jpedsurg.2011.08.003. PMID: 22325405.	Wrong population: Children
Lal G, Duh QY. Laparoscopic adrenalectomy--indications and technique. Surg Oncol. 2003 Aug;12(2):105-23. doi: 10.1016/s0960-7404(03)00036-7. PMID: 12946482.	Wrong design: Narrative review

Literature search strategy

Algemene informatie

Richtlijn: Diagnostiek en behandeling van bijniertumoren	
Uitgangsvraag: Welke benadering bij minimaal invasieve chirurgie heeft de voorkeur voor het verwijderen van een bijniertumor?	
Database(s): Ovid/Medline, Embase	Datum: 7-4-2022
Periode: 2000-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de elementen bijniertumoren en adrenalectomie. Specifiek zoeken op transperitoneal of laparoscopic of retroperitoneal gaf 10 referenties minder in het resultaat, vandaar dat gekozen is om breed te zoeken op adrenalectomie Alle sleutelartikelen worden gevonden	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 7-4-2022 met relevante zoektermen gezocht naar systematische reviews en RCTs over adrenalectomie van bijniertumoren. De literatuurzoekactie leverde 219 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	144	119	186
RCTs	66	81	33
Observationele studies			
Overig			
Totaal			219

Zoekstrategie

Embase

No.	Query	Results
#14	#4 AND (#12 OR #13) Sleutelartikelen gevonden	4
#13	#12 NOT #11 RCT	66
#12	#8 AND #10	82
#11	#8 AND #9 SR	144
#10	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1897667

No.	Query	Results
#9	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	815025
#8	#7 AND [1-1-2000]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	3859
#7	#5 AND #6	7101
#6	'adrenalectomy'/exp OR adrenalectom*:ti,ab,kw	34002
#5	'adrenal cortex carcinoma'/exp OR 'adrenal cancer'/exp OR 'suprarenal carcinoma':ti,ab,kw OR (((adren* OR suprarenal) NEAR/4 (cancer* OR neoplasm* OR carcinoma* OR lesion* OR tumor* OR disease*)):ti,ab,kw) OR 'adrenal enucleation':ti,ab,kw OR 'hemiadrenalectomy':ti,ab,kw	31684
#4	#1 OR #2 OR #3	4
#3	prospective, AND randomized AND comparison AND of AND transperitoneal AND versus AND retroperit oneal AND laparoscopic AND adrenalectomy AND rubinstein	1
#2	lateral AND transperitoneal AND versus AND posterior AND retroperitoneoscopic AND adrenalectomy A ND for AND benign AND adrenal AND gland AND disease AND randomized AND controlled AND trial AN D at AND a AND single AND tertiary AND medical AND center	1
#1	randomized AND clinical AND trial AND of AND posterior AND retroperitoneoscopic AND versus AND lat eral AND transperitoneal AND laparoscopic AND adrenalectomy AND with AND a AND '5 year' AND 'follow up'	2

Ovid/Medline

#	Searches	Results
10	9 not 8 RCT	81
9	5 and 7	99
8	5 and 6 SR	119
7	(exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.) not (animals/ not humans/)	1364804
6	(meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	557229
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	4408
4	limit 3 to yr="2000 -Current"	4685
3	1 and 2	6954
2	Adrenalectomy/ or adrenalectom*.ti,ab,kf.	26891
1	exp Adrenal Gland Neoplasms/ or suprarenal carcinoma.ti,ab,kf. or ((adren* or suprarenal) adj4 (cancer* or neoplasm* or carcinoma* or tumor* or lesion* or disease*)).ti,ab,kf.	40769

Module 11 – Genetisch testen en chirurgisch beleid

Uitgangsvraag
Hoe beïnvloedt genetisch testen het chirurgisch beleid bij patiënten met een bijniertumor (feochromocytoom/paraganglioom)?

Inleiding
Volgens landelijke consensus wordt met alle patiënten met een paraganglioom in het hoofdhalsgebied en alle patiënten met een feochromocytoom onder de 50 jaar etiologisch genetisch onderzoek besproken. Bij 30-50% van de feochromocytomen blijkt er sprake van een erfelijke aanleg (Garcia-Carbonero, 2021). Tussen de 5-10% van de volwassen patiënten krijgt ook een controlateraal feochromocytoom (en 35-40% van de kinderen). Bij bilateraal feochromocytoom wordt gerapporteerd dat 80% een genetische aanleg kan worden aangetoond, meestal MEN2A syndroom (Kittah, 2020). Als er op voorhand een genetische oorzaak voor het feochromocytoom bekend is, wordt bij voorkeur cortex sparend geopereerd*, vanwege een verhoogde kans op een contralateraal feochromocytoom. Bij patiënten van wie geen genetische aanleg bekend is, is daarom DNA–onderzoek voorafgaand aan de operatie mogelijk zinvol, om zo het beleid eventueel te kunnen aanpassen.
**M.u.v. pathogene SDHB mutatie i.v.m. verhoogd risico op lokaal recidief en/of metastasering*

Search and select
A systematic review of the literature was performed to answer the following question:
What is the effect of an adjusted surgical policy after preoperatively known genetic test results compared to a standard surgical policy without preoperatively known genetic test results in patients with a pheochromocytoma with unknown genetic status?

P (Patients)	patients with a pheochromocytoma with unknown genetic status
I (Intervention)	genetic test results are known before the surgery, the surgical policy is adjusted based on the test results
C (Control)	genetic test results are not known before the surgery, standard surgical policy is followed
O (Outcomes)	efficacy (clinically and hormonally cured), recurrent disease, metastases

Relevant outcome measures
The guideline development group considered efficacy, recurrent disease, and metastases as critical outcome measures for decision making.

The working group defined the outcome measures as follows:
- Efficacy: clinically and hormonally cured with maintenance of hormonal production in the adrenal cortex
- Recurrent disease: the development of another (contralateral) primary pheochromocytoma (or extra adrenal paraganglioma)
- Metastases: the development of secondary malignant growths at a distance from a primary pheochromocytoma

The working group defined the following differences as a minimal clinically (patient) important difference:
- Efficacy: Absolute difference >5%, or absolute difference >3% and HR <0.7
- Recurrent disease: Absolute difference >5%, or absolute difference >3% and HR <0.7
- Metastases: Absolute difference >5%, or absolute difference >3% and HR <0.7

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2010 until 18-08-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 555 hits. Studies were selected based on the following criteria:

- Systematic reviews, randomized controlled trials, or observational comparative studies;
- Full-text English or Dutch language publication;
- Complying with the PICO criteria.

Thirty-eight studies were initially selected based on title and abstract screening. After reading the full text, 38 studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Results
No studies were included in the analysis of the literature.

Summary of literature
Description of studies
Not applicable.

Results
Efficacy (clinically and hormonally cured), recurrent disease, metastases
No studies were found that compared an adjusted surgical policy after preoperatively known genetic test results compared to a standard surgical policy without preoperatively known genetic test results in patients with a pheochromocytoma with unknown genetic status on the outcomes: efficacy (clinically and hormonally cured), recurrent disease and metastases.

Level of evidence of the literature
Efficacy (clinically and hormonally cured), recurrent disease, metastases
The level of evidence for the comparison of an adjusted surgical policy after preoperatively known genetic test results versus a standard surgical policy without preoperatively known genetic test results in patients with a pheochromocytoma with unknown genetic status could not be assessed for the outcomes: efficacy (clinically and hormonally cured), recurrent disease and metastases since no appropriate studies were found.

Conclusions
Efficacy (clinically and hormonally cured), recurrent disease, metastases

- **GRADE**	No studies were found that compared an adjusted surgical policy after preoperatively known genetic test results compared to a standard surgical policy without preoperatively known genetic test results in patients with a pheochromocytoma with unknown genetic status on the outcomes: efficacy (clinically and hormonally cured), recurrent disease and metastases. *Source: -*

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

Patiënten met een feochromocytoom onder de 50 jaar komen volgens de richtlijn nu al in aanmerking voor een DNA-onderzoek naar erfelijke oorzaken hiervoor en in de praktijk wordt aan alle patiënten met een paraganglioom ongeacht de leeftijd een diagnostisch DNA-panel onderzoek aangeboden. De uitslag van het onderzoek bepaalt beleid en follow-up voor de patiënt en de mogelijkheden voor familieonderzoek.
De literatuur over de invloed van genetisch testen op het aanpassen van het chirurgisch beleid bij patiënten met een feochromocytoom is erg beperkt. De literatuursearch leverde geen artikelen op waarin een aangepast chirurgisch beleid op basis van een preoperatief bekende genetische uitslag werd vergeleken met een standaard chirurgisch beleid zonder een preoperatief bekende genetische uitslag. Op basis van de gevonden studies is het dus onzeker of genetisch testen (bij patiënten van wie geen genetische aanleg bekend is) voorafgaand aan de operatie en het daarop aanpassen van het chirurgisch beleid effectief is.

De studie van Nockel (2018) werd niet geïncludeerd voor de literatuursamenvatting omdat deze niet aan de PICO voldeed. Echter sluit de scope van dit artikel wel aan bij het onderwerp van deze module. Nockel (2018) beschrijft zijn onderzoek waarbij preoperatief genetisch testen meegenomen wordt om de operatieve strategie (open versus laparascopisch en cortex sparend versus adrenalectomie) aan te passen bij patiënten met een feochromocytoom of paraganglioom. Daarvoor werd een retrospectieve analyse gedaan van 108 patiënten met een histologische diagnose feochromocytoom of paraganglioom die een resectie ondergingen. Ze werden preoperatief getest op een aantal predispositiegenen (RET, VHL, NF1, SDHA-D, MAX en FH). Bij 47% (n=51) van de patiënten werd een kiembaanmutatie gevonden. Hiervan was er bij 33% (n=17) geen familiegeschiedenis bekend. De aanwezigheid van een kiembaanmutatie werd meegenomen om de operatieve strategie voor resectie van het feochromocytoom te bepalen, zowel voor patiënten met als zonder bekende familiegeschiedenis. De laatste groep betrof tien patiënten voor wie het een eerste operatie was en zeven patiënten voor wie het een heroperatie was. Bij drie patiënten werd een minimaal invasieve benadering gebruikt. Er werd een laparoscopische adrenalectomie gedaan bij twee patiënten met een RET-mutatie hoewel de maximale diameter van hun tumoren 9.5 en 8 centimeter waren, omdat er een laag risico op metastasen was. Er werd een laparoscopische resectie van een paraganglioom gedaan bij één patiënt met een VHL-mutatie. Tot slot werd er bij vijf patiënten een open adrenalectomie gedaan omdat zij een SDHB of FH-mutatie hadden.
Over de benadering bij een bekende genetische predispositie is wel literatuur beschikbaar, die aangeeft dat de operatieve strategie daarop kan worden aangepast (Castinetti, 2015; Rossitti, 2018). Bij MEN2A werd bij de groep patiënten die een unilaterale subtotale adrenalectomie ondergingen een vergelijkbare recidiefkans en op termijn minder complicaties (steroïde vervangingstherapie) gezien, in vergelijking tot de patiënten bij wie een unilaterale totale adrenalectomie werd verricht (Scholten, 2011).

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Patiënten met feochromocytoom, ook als er geen familiare belasting bekend is of als er geen erfelijke aanleg bekend is komen in aanmerking voor DNA-onderzoek en verwijzing naar de klinisch geneticus. De uitkomst van een DNA-onderzoek heeft invloed op het beleid en de follow up voor de patiënt, maar kan ook van betekenis zijn voor de (naaste) familie. Familieleden die drager zijn van dezelfde genetische aanleg komen in aanmerking voor een specifiek surveillance advies, waarbij patiënten periodiek gecontroleerd worden op aandoeningen die beschreven zijn bij het betreffende syndroom. Dit advies wordt door geneticus in overleg met multidisciplinair team opgesteld en patiënten worden door geneticus verwezen naar chirurg/endocrinoloog (VKGN/StOET richtlijnen boekje, Stichting opsporing erfelijke tumoren (stoet.nl)). Verwijzing naar de klinische genetica en DNA-onderzoek op het

moment dat de diagnose feochromocytoom/paraganglioom is gesteld is altijd in overleg en met informed consent.

Aanvragen van het diagnostische DNA onderoek kan volgens lokale afspraken hierover door de klinische genetica of een andere zorgprofessional worden aangevraagd, waarbij pre-test counseling geborgd is.

Kosten (middelenbeslag)
Er is een indicatie voor DNA-onderzoek bij alle patiënten met een feochromocytoom of paraganglioom ongeacht de leeftijd of tumorkarakteristieken. Alleen de timing van het onderzoek en de uitslagtermijn wordt aangepast. Een spoed DNA-onderzoek brengt op zich niet meer kosten met zich mee, alleen een verschuiving in het werkproces. Daarnaast gaat het om relatief kleine aantallen.

Aanvaardbaarheid, haalbaarheid en implementatie
Met de individuele afdelingen Genetica van de diverse academische centra moeten afspraken worden gemaakt over spoedverwijzing en spoeddiagnostiek en mogelijkheid/wenselijkheid van aanvragen DNA-onderzoek door niet-klinisch genetici (consent en schriftelijke informatie). Dit is voor andere genetische aandoeningen al een reguliere werkwijze, daarom kan dit naar verwachting probleemloos geïmplementeerd worden.

Aanbevelingen
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Er is veel literatuur beschikbaar welke ingaat op optimale operatie strategie, gebaseerd op bijvoorbeeld grootte van de afwijking, maar ook voor de verschillende erfelijke feochromocytoom/paraganglioom oorzaken.
Alle patiënten met een paraganglioom en ook met feochromocytoom (bij deze tumor in elk geval met een presentatie jonger dan 50 jaar) komen in aanmerking voor een diagnostisch DNA-onderzoek van een panel met meerdere predispositie genen.
Er is geen vergelijkend onderzoek beschikbaar, maar wel een studie die beschrijft dat de operatie strategie mede bepaald wordt door de uitslag van een DNA-panel test, waarin de eerder beschreven uitkomstmaten niet verschillen ook niet voor de erfelijk belaste patiënten bij wie vooraf geen verdenking was dat het feochromocytoom erfelijk zou kunnen zijn.

Verricht de DNA-diagnostiek van bekende predispositiegenen, waarvoor alle patiënten met feochromocytoom en paraganglioom op een andere locatie in aanmerking komen en van wie tevoren niet bekend was dat zij een erfelijke aanleg hebben, bij voorkeur voorafgaand aan de operatieve ingreep zodat kan de chirurgische interventie mede op deze uitslag worden gebaseerd.

Literatuur
Castinetti F, Taieb D, Henry JF, Walz M, Guerin C, Brue T, Conte-Devolx B, Neumann HP, Sebag F. MANAGEMENT OF ENDOCRINE DISEASE: Outcome of adrenal sparing surgery in heritable pheochromocytoma. Eur J Endocrinol. 2016 Jan;174(1):R9-18. doi: 10.1530/EJE-15-0549. Epub 2015 Aug 21. PMID: 26297495.

Garcia-Carbonero R, Matute Teresa F, Mercader-Cidoncha E, Mitjavila-Casanovas M, Robledo M, Tena I, Alvarez-Escola C, Arístegui M, Bella-Cueto MR, Ferrer-Albiach C, Hanzu FA. Multidisciplinary practice guidelines for the diagnosis, genetic counseling and treatment of pheochromocytomas and paragangliomas. Clin Transl Oncol. 2021 Oct;23(10):1995-2019.

doi: 10.1007/s12094-021-02622-9. Epub 2021 May 6. PMID: 33959901; PMCID: PMC8390422.

Kittah NE, Gruber LM, Bancos I, Hamidi O, Tamhane S, Iñiguez-Ariza N, Babovic-Vuksanovic D, Thompson GB, Lteif A, Young WF, Erickson D. Bilateral pheochromocytoma: Clinical characteristics, treatment and longitudinal follow-up. Clin Endocrinol (Oxf). 2020 Sep;93(3):288-295. doi: 10.1111/cen.14222. Epub 2020 Jun 22. PMID: 32410303.

Nockel P, El Lakis M, Gaitanidis A, Yang L, Merkel R, Patel D, Nilubol N, Prodanov T, Pacak K, Kebebew E. Preoperative genetic testing in pheochromocytomas and paragangliomas influences the surgical approach and the extent of adrenal surgery. Surgery. 2018 Jan;163(1):191-196. doi: 10.1016/j.surg.2017.05.025. Epub 2017 Nov 7. PMID: 29126554; PMCID: PMC5736453.

Rossitti HM, Söderkvist P, Gimm O. Extent of surgery for phaeochromocytomas in the genomic era. Br J Surg. 2018 Jan;105(2):e84-e98. doi: 10.1002/bjs.10744. PMID: 29341163.

Scholten A, Valk GD, Ulfman D, Borel Rinkes IH, Vriens MR. Unilateral subtotal adrenalectomy for pheochromocytoma in multiple endocrine neoplasia type 2 patients: a feasible surgical strategy. Ann Surg. 2011 Dec;254(6):1022-7. doi: 10.1097/SLA.0b013e318237480c. PMID: 22107743.

Bijlagen bij module Genetisch testen en chirurgisch beleid

Evidence tables
Not applicable.

Table of excluded studies

Reference	Reason for exclusion
Angelousi A, Kassi E, Zografos G, Kaltsas G. Metastatic pheochromocytoma and paraganglioma. Eur J Clin Invest. 2015 Sep;45(9):986-97. doi: 10.1111/eci.12495. PMID: 26183460.	Systematic review with different PICO.
Assadipour Y, Sadowski SM, Alimchandani M, Quezado M, Steinberg SM, Nilubol N, Patel D, Prodanov T, Pacak K, Kebebew E. SDHB mutation status and tumor size but not tumor grade are important predictors of clinical outcome in pheochromocytoma and abdominal paraganglioma. Surgery. 2017 Jan;161(1):230-239. doi: 10.1016/j.surg.2016.05.050. Epub 2016 Nov 10. PMID: 27839933; PMCID: PMC5164946.	Predicitive model.
Barski D. Management and follow up of extra-adrenal phaeochromocytoma. Cent European J Urol. 2014;67(2):156-61. doi: 10.5173/ceju.2014.02.art8. Epub 2014 Jun 23. PMID: 25140230; PMCID: PMC4132600.	Narrative review.
Bausch B, Wellner U, Bausch D, Schiavi F, Barontini M, Sanso G, Walz MK, Peczkowska M, Weryha G, Dall'igna P, Cecchetto G, Bisogno G, Moeller LC, Bockenhauer D, Patocs A, Rácz K, Zabolotnyi D, Yaremchuk S, Dzivite-Krisane I, Castinetti F, Taieb D, Malinoc A, von Dobschuetz E, Roessler J, Schmid KW, Opocher G, Eng C, Neumann HP. Long-term prognosis of patients with pediatric pheochromocytoma. Endocr Relat Cancer. 2013 Dec 16;21(1):17-25. doi: 10.1530/ERC-13-0415. PMID: 24169644.	Prognostic study.
Brito JP, Asi N, Bancos I, Gionfriddo MR, Zeballos-Palacios CL, Leppin AL, Undavalli C, Wang Z, Domecq JP, Prustsky G, Elraiyah TA, Prokop LJ, Montori VM, Murad MH. Testing for germline mutations in sporadic pheochromocytoma/paraganglioma: a systematic review. Clin Endocrinol (Oxf). 2015 Mar;82(3):338-45. doi: 10.1111/cen.12530. Epub 2014 Jul 7. PMID: 24954084.	Systematic review with different PICO.
Butz JJ, Yan Q, McKenzie TJ, Weingarten TN, Cavalcante AN, Bancos I, Young WF Jr, Schroeder DR, Martin DP, Sprung J. Perioperative outcomes of syndromic paraganglioma and pheochromocytoma resection in patients with von Hippel-Lindau disease, multiple endocrine neoplasia type 2, or neurofibromatosis type 1. Surgery. 2017 Dec;162(6):1259-1269. doi:	Wrong comparison (MEN2, VHL and NF1).

10.1016/j.surg.2017.08.002. Epub 2017 Sep 14. PMID: 28919049.	
Castinetti F, Taieb D, Henry JF, Walz M, Guerin C, Brue T, Conte-Devolx B, Neumann HP, Sebag F. MANAGEMENT OF ENDOCRINE DISEASE: Outcome of adrenal sparing surgery in heritable pheochromocytoma. Eur J Endocrinol. 2016 Jan;174(1):R9-18. doi: 10.1530/EJE-15-0549. Epub 2015 Aug 21. PMID: 26297495.	No comparison.
Därr R, Lenders JW, Hofbauer LC, Naumann B, Bornstein SR, Eisenhofer G. Pheochromocytoma - update on disease management. Ther Adv Endocrinol Metab. 2012 Feb;3(1):11-26. doi: 10.1177/2042018812437356. PMID: 23148191; PMCID: PMC3474647.	Narrative review.
De Filpo G, Cantini G, Rastrelli G, Vannini G, Ercolino T, Luconi M, Mannelli M, Maggi M, Canu L. Management and outcome of metastatic pheochromocytomas/paragangliomas: a monocentric experience. J Endocrinol Invest. 2022 Jan;45(1):149-157. doi: 10.1007/s40618-021-01629-x. Epub 2021 Jul 5. PMID: 34227051; PMCID: PMC8741659.	No comparison.
Ellis RJ, Patel D, Prodanov T, Nilubol N, Pacak K, Kebebew E. The presence of SDHB mutations should modify surgical indications for carotid body paragangliomas. Ann Surg. 2014 Jul;260(1):158-62. doi: 10.1097/SLA.0000000000000283. PMID: 24169168; PMCID: PMC6980248.	Wrong population (only paragangliomas).
Fishbein L, Merrill S, Fraker DL, Cohen DL, Nathanson KL. Inherited mutations in pheochromocytoma and paraganglioma: why all patients should be offered genetic testing. Ann Surg Oncol. 2013 May;20(5):1444-50. doi: 10.1245/s10434-013-2942-5. Epub 2013 Mar 20. PMID: 23512077; PMCID: PMC4291281.	Prevalence study.
Grubbs EG, Rich TA, Ng C, Bhosale PR, Jimenez C, Evans DB, Lee JE, Perrier ND. Long-term outcomes of surgical treatment for hereditary pheochromocytoma. J Am Coll Surg. 2013 Feb;216(2):280-9. doi: 10.1016/j.jamcollsurg.2012.10.012. PMID: 23317575.	Wrong comparison.
Gupta A, Agarwala S, Tandon N, Srinivas M, Bajpai M, Gupta DK, Gupta AK, Bal C, Kumar R, Bhatnagar V. Pheochromocytoma management, outcomes and the role of cortical preservation. Indian J Pediatr. 2014 Aug;81(8):780-4. doi: 10.1007/s12098-013-1283-5. Epub 2013 Nov 8. PMID: 24197525.	No comparison.
Holland J, Chandurkar V. A retrospective study of surgically excised phaeochromocytomas in Newfoundland, Canada. Indian J Endocrinol Metab. 2014 Jul;18(4):542-5. doi: 10.4103/2230-8210.137514. PMID: 25143914; PMCID: PMC4138913.	No comparison.

Horton C, LaDuca H, Deckman A, Durda K, Jackson M, Richardson ME, Tian Y, Yussuf A, Jasperson K, Else T. Universal Germline Panel Testing for Individuals With Pheochromocytoma and Paraganglioma Produces High Diagnostic Yield. J Clin Endocrinol Metab. 2022 Apr 19;107(5):e1917-e1923. doi: 10.1210/clinem/dgac014. PMID: 35026032; PMCID: PMC9016434.	Wrong intervention (no surgical policy).
Iacobone M, Schiavi F, Bottussi M, Taschin E, Bobisse S, Fassina A, Opocher G, Favia G. Is genetic screening indicated in apparently sporadic pheochromocytomas and paragangliomas? Surgery. 2011 Dec;150(6):1194-201. doi: 10.1016/j.surg.2011.09.024. PMID: 22136840.	Wrong intervention (no surgical policy).
Johnston PC, Mullan KR, Atkinson AB, Eatock FC, Wallace H, Gray M, Hunter SJ. Recurrence of Phaeochromocytoma and Abdominal Paraganglioma After Initial Surgical Intervention. Ulster Med J. 2015 May;84(2):102-6. PMID: 26170485; PMCID: PMC4488930.	No comparison.
Kuo MJM, Nazari MA, Jha A, Pacak K. Pediatric Metastatic Pheochromocytoma and Paraganglioma: Clinical Presentation and Diagnosis, Genetics, and Therapeutic Approaches. Front Endocrinol (Lausanne). 2022 Jul 12;13:936178. doi: 10.3389/fendo.2022.936178. PMID: 35903274; PMCID: PMC9314859.	No comparison.
Lee H, Jeong S, Yu Y, Kang J, Sun H, Rhee JK, Kim YH. Risk of metastatic pheochromocytoma and paraganglioma in SDHx mutation carriers: a systematic review and updated meta-analysis. J Med Genet. 2020 Apr;57(4):217-225. doi: 10.1136/jmedgenet-2019-106324. Epub 2019 Oct 24. PMID: 31649053.	Systematic review with different PICO.
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1456. doi: 10.1097/HJH.0000000000002438. PMID: 32412940; PMCID: PMC7486815.	
Maignan A, Guerin C, Julliard V, Paladino NC, Kim E, Roche P, Castinetti F, Essamet W, Mancini J, Imperiale A, Clifton-Bligh R, Romanet P, Barlier A, Pacak K, Sebag F, Taïeb D. Implications of SDHB genetic testing in patients with sporadic pheochromocytoma. Langenbecks Arch Surg. 2017 Aug;402(5):787-798. doi: 10.1007/s00423-017-1564-y. Epub 2017 Feb 22. PMID: 28229225; PMCID: PMC7440815.	Wrong comparison.
Main AM, Rossing M, Borgwardt L, Grønkær Toft B, Rasmussen ÅK, Feldt-Rasmussen U. Genotype-phenotype associations in PPGLs in 59 patients with variants in SDHX genes. Endocr Connect. 2020 Aug;9(8):793-803. doi: 10.1530/EC-20-0279. PMID: 32688340; PMCID: PMC7487185.	Genotype-phenotype association study.
Martins D, Rodrigues D, Melo M, Carrilho F. Laparoscopic adrenalectomy as an effective approach to massive bilateral pheochromocytomas. BMJ Case Rep. 2017 Sep 7;2017:bcr2017221009. doi: 10.1136/bcr-2017-221009. PMID: 28883010; PMCID: PMC5604699.	Case report.
Muth A, Abel F, Jansson S, Nilsson O, Ahlman H, Wängberg B. Prevalence of germline mutations in patients with pheochromocytoma or abdominal paraganglioma and sporadic presentation: a population-based study in Western Sweden. World J Surg. 2012 Jun;36(6):1389-94. doi: 10.1007/s00268-012-1430-6. PMID: 22270996; PMCID: PMC3348434.	No comparison.
Nockel P, El Lakis M, Gaitanidis A, Yang L, Merkel R, Patel D, Nilubol N, Prodanov T, Pacak K, Kebebew E. Preoperative genetic testing in pheochromocytomas and paragangliomas influences the surgical approach and the extent of adrenal surgery. Surgery. 2018 Jan;163(1):191-196. doi: 10.1016/j.surg.2017.05.025. Epub 2017 Nov 7. PMID: 29126554; PMCID: PMC5736453.	Wrong comparison.
Parasiliti-Caprino M, Bioletto F, Lopez C, Maletta F, Caputo M, Gasco V, La Grotta A, Limone P, Borretta G, Volante M, Papotti M, Terzolo M, Morino M, Pasini B, Veglio F, Ghigo E, Arvat E, Maccario M. Development and internal validation of a predictive model for the estimation of pheochromocytoma recurrence risk after radical surgery. Eur J Endocrinol. 2022 Feb 15;186(3):399-406. doi: 10.1530/EJE-21-0370. PMID: 35363157.	Predictive model.
Parasiliti-Caprino M, Lucatello B, Lopez C, Burrello J, Maletta F, Mistrangelo M, Migliore E, Tassone F, La Grotta A, Pia A, Reimondo G, Giordano R, Giraudo G, Piovesan A, Ciccone G, Deandreis D, Limone P, Orlandi F, Borretta G, Volante M, Mulatero P, Papotti M,	Predictive model.

Aimaretti G, Terzolo M, Morino M, Pasini B, Veglio F, Ghigo E, Arvat E, Maccario M. Predictors of recurrence of pheochromocytoma and paraganglioma: a multicenter study in Piedmont, Italy. Hypertens Res. 2020 Jun;43(6):500-510. doi: 10.1038/s41440-019-0339-y. Epub 2019 Oct 4. PMID: 31586159.	
Parisien-La Salle S, Dumas N, Bédard K, Jolin J, Moramarco J, Lacroix A, Lévesque I, Burnichon N, Gimenez-Roqueplo AP, Bourdeau I. Genetic spectrum in a Canadian cohort of apparently sporadic pheochromocytomas and paragangliomas: New data on multigene panel retesting over time. Clin Endocrinol (Oxf). 2022 Jun;96(6):803-811. doi: 10.1111/cen.14618. Epub 2021 Nov 8. PMID: 34750850.	Genetic analysis, prevalence study.
Persu A, Lannoy N, Maiter D, Mendola A, Montigny P, Oriot P, Vinck W, Garin P, Hamoir M, Vikkula M. Prevalence and spectrum of SDHx mutations in pheochromocytoma and paraganglioma in patients from Belgium: an update. Horm Metab Res. 2012 May;44(5):349-53. doi: 10.1055/s-0032-1311610. Epub 2012 May 7. PMID: 22566194.	Prevalence study.
Petri BJ, van Eijck CH, de Herder WW, Wagner A, de Krijger RR. Phaeochromocytomas and sympathetic paragangliomas. Br J Surg. 2009 Dec;96(12):1381-92. doi: 10.1002/bjs.6821. PMID: 19918850.	Systematic review with different PICO.
Pipitprapat W, Pattanaprateep O, Iemwimangsa N, Sensorn I, Panthan B, Jiaranai P, Chantratita W, Sorapipatcharoen K, Poomthavorn P, Mahachoklertwattana P, Sura T, Tunteeratum A, Srichan K, Sriphrapradang C. Cost-minimization analysis of sequential genetic testing versus targeted next-generation sequencing gene panels in patients with pheochromocytoma and paraganglioma. Ann Med. 2021 Dec;53(1):1243-1255. doi: 10.1080/07853890.2021.1956687. PMID: 34309460; PMCID: PMC8317928.	Cost-minimization analysis.
Sbardella E, Cranston T, Isidori AM, Shine B, Pal A, Jafar-Mohammadi B, Sadler G, Mihai R, Grossman AB. Routine genetic screening with a multi-gene panel in patients with pheochromocytomas. Endocrine. 2018 Jan;59(1):175-182. doi: 10.1007/s12020-017-1310-9. Epub 2017 May 5. PMID: 28477304.	Wrong intervention (no surgical policy).
Tarallo M, Crocetti D, Cavallaro G, Caruso D, Chiappini A, Petramala L, Sapienza P, Letizia C, Fiori E, De Toma G. Surgical treatment and management of syndromic paraganglioma. The experience of a referral center. Ann Ital Chir. 2021;92:465-470. PMID: 34569475.	No full-text availability (Italian).
Tufton N, Sahdev A, Drake WM, Akker SA. Can subunit-specific phenotypes guide surveillance	Narrative review.

imaging decisions in asymptomatic SDH mutation carriers? Clin Endocrinol (Oxf). 2019 Jan;90(1):31-46. doi: 10.1111/cen.13877. Epub 2018 Nov 28. PMID: 30303539.	
Uslar T, San Francisco IF, Olmos R, Macchiavelo S, Zuñiga A, Rojas P, Garrido M, Huete A, Mendez GP, Cortinez I, Zemelman JT, Cifuentes J, Castro F, Olivari D, Domínguez JM, Arteaga E, Fardella CE, Valdés G, Tagle R, Baudrand R. Clinical Presentation and Perioperative Management of Pheochromocytomas and Paragangliomas: A 4-Decade Experience. J Endocr Soc. 2021 Apr 22;5(10):bvab073. doi: 10.1210/jendso/bvab073. PMID: 34377881; PMCID: PMC8336720.	Wrong comparison (between four decades).
Waldmann J, Patsalis N, Fendrich V, Langer P, Saeger W, Chaloupka B, Ramaswamy A, Fassnacht M, Bartsch DK, Slater EP. Clinical impact of TP53 alterations in adrenocortical carcinomas. Langenbecks Arch Surg. 2012 Feb;397(2):209-16. doi: 10.1007/s00423-011-0868-6. Epub 2011 Dec 29. PMID: 22203015.	No comparison.
Younes A, Elgendy A, Zekri W, Fadel S, Elfandy H, Romeih M, Azer M, Ahmed G. Operative management and outcomes in children with pheochromocytoma. Asian J Surg. 2022 Jan;45(1):419-424. doi: 10.1016/j.asjsur.2021.07.029. Epub 2021 Jul 27. PMID: 34325990.	No comparison.

Literature search strategy

Algemene informatie

Richtlijn: NVVH Bijniertumoren	
Uitgangsvraag: UV12 Hoe beïnvloedt genetisch testen het chirurgisch beleid bij patiënten met een bijniertumor?	
Database(s): Ovid/Medline, Embase	Datum: 18-8-2022
Periode: 2010-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: Pheochromocytoma EN (genetic testing OR genomics) In overleg met de adviseur is afgesproken dat molecular diagnostics niet wordt meegenomen. Van de drie sleutelartikelen wordt uiteindelijk alleen het artikel van Rossitti gevonden. Het artikel van Scholten wordt niet gevonden omdat in title, abstract en indexterms niet wordt gesproken over genetic screening. Het artikel van Castinetti wordt niet gevonden omdat het een abstract journal betreft wat niet wordt opgenomen in deze databases. Omdat het artikel van Rossitti in eerste instantie niet werd gevonden is besloten de term genomics toe te voegen aan de strategie. Omdat de gevonden aantallen te overzien zijn en de nadruk ligt op het testen en er altijd een chirurgische ingreep plaatsvindt, wordt besloten om chirurgie niet mee te nemen in de strategie.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 18-8-2022 met relevante zoektermen gezocht naar systematische reviews, RCTs en observationele studies over het genetisch testen bij patiënten met pheochromocytoma. De literatuurzoekactie leverde 555 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	39	48	70
RCTs	4	11	14
Observationele studies	321	292	471
Overig			
Totaal			555

Zoekstrategie

Embase

No.	Query	Results
#21	#19 NOT #18 NOT #17 OBS	321
#20	#18 NOT #17 RCT	4
#19	#10 AND #16	335
#18	#10 AND #13	8
#17	#10 AND #12 SR	39
#16	#14 OR #15	15117057
#15	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	13364261
#14	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	7199076
#13	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1946023
#12	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	849601
#11	#9 AND #10 Sleutelartikel Rossitti gevonden	2
#10	#3 AND [1-1-2010]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	968

No.	Query	Results
#9	#6 OR #7 OR #8	3
#8	unilateral AND subtotal AND adrenalectomy AND for AND pheochromocytoma AND in AND multiple AN D endocrine AND neoplasia AND type AND 2 AND patients AND scholten	1
#7	outcome AND adrenal AND sparing AND surgery AND in AND heritable AND pheochromocytoma AND th e AND example AND of AND multiple AND endocrine AND neoplasia AND type AND 2	0
#6	extent AND of AND surgery AND for AND phaeochromocytomas AND in AND the AND genomic AND era	2
#5	#3 AND #4	1431
#4	'surgery'/exp OR 'surgery'/lnk OR surgical:ti,ab,kw OR surger*:ti,ab,kw OR operation*:ti,ab,kw OR operative:ti,ab,kw OR 'unilateral adrenalectomy'/exp OR (((hemi OR monolateral OR unilateral OR 'cortical sparing' OR subtotal OR partial) NEAR/3 adrenalectom*):ti,ab,kw) OR 'hemiadrenalectomy':ti,ab,kw	7143238
#3	#1 AND #2	3606
#2	'genetic screening'/exp OR 'genomics'/exp OR (((genetic* OR genomic* OR genotyp*) NEAR/5 (screen* OR test* OR analys* OR assess* OR evaluat*)):ti,ab,kw)	516012
#1	'pheochromocytoma'/exp OR 'chromaffin cell tumor':ti,ab,kw OR 'chromaffin paraganglioma':ti,ab,kw OR 'phaeochromoblastoma':ti,ab,kw OR 'phaeochromocytoma':ti,ab,kw OR 'pheochromoblastoma':ti,ab,kw OR 'pheochromocytoma':ti,ab,kw OR 'pheochromocytomata':ti,ab,kw OR 'pheochromocytomatosis':ti,ab,kw OR 'pheochromocytosis':ti,ab,kw OR ((catecholamine NEAR/4 (tumour* OR tumor* OR neoplasm*)):ti,ab,kw) OR ('neoplasm'/exp AND 'adrenal gland'/exp) OR (((adrenal OR suprarenal) NEAR/3 (gland OR medulla) NEAR/4 (cancer* OR tumour* OR tumor* OR neoplasm* OR malignan*)):ti,ab,kw)	45515

Ovid/Medline

#	Searches	Results
14	12 not 11 not 10 OBS	292
13	11 not 10 RCT	11
12	5 and (8 or 9)	316
11	5 and 7	12
10	5 and 6 SR	48
9	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5225241
8	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4223215
7	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1537965
6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data	611913

	extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1079
4	limit 3 to yr="2010 -Current"	1242
3	1 and 2	2092
2	exp Genetic Testing/ or exp Genomics/ or ((genetic* or genomic* or genotyp*) adj5 (screen* or test* or analys* or assess* or evaluat*)).ti,ab,kf.	425264
1	exp Adrenal Gland Neoplasms/ or Adrenalectomy/ or exp Catecholamines/ or Pheochromocytoma/ or phaeochromo*.ti,ab,kf. or pheochromo*.ti,ab,kf. or chromaffin cell tumor.ti,ab,kf. or chromaffin paraganglioma.ti,ab,kf. or phaeochromoblastoma.ti,ab,kf. or phaeochromocytoma.ti,ab,kf. or pheochromoblastoma.ti,ab,kf. or pheochromocytoma.ti,ab,kf. or pheochromocytomata.ti,ab,kf. or pheochromocytomatosis.ti,ab,kf. or pheochromocytosis.ti,ab,kf. or (catecholamine adj4 (tumour* or tumor* or neoplasm*)).ti,ab,kf. or ((adrenal or suprarenal) adj3 (gland or medulla) adj4 (cancer* or tumour* or tumor* or neoplasm* or malignan*)).ti,ab,kf.	317982

Module 12 – Pathologieverslag

Uitgangsvraag
Welke informatie dient het standaard pathologieverslag voor bijnierschorscarcinoom en feochromocytoom* ten minste te bevatten?

** Feochromocytoom wordt in deze module gedefineerd als een neuroendocriene tumor uitgaande van chromaffine cellen van het bijniermerg en wordt beschouwd als intra-adrenaal paraganglioom.*

Inleiding
Voor een optimale diagnose en behandeling van het bijnierschorscarcinoom en feochromocytoom is het essentieel dat alle relevante klinische, macroscopische en microscopische aspecten bij pathologisch onderzoek worden geëvalueerd. Het onderzoek moet vervolgens worden gerapporteerd op basis van erkende definities en op een gestandaardiseerde wijze.

Search and select
There was no systematic search performed because the question was not suitable to conform to the Patient Intervention Comparison Outcome (PICO) question. International guidelines and consensus documents regarding this topic, submitted by the working group members, are summarized and used to answer this question.

Search and select (Methods)
Not applicable.

Results
No studies were included in the analysis of the literature.

Summary of literature
Description of studies
Not applicable.

Results
Not applicable.

Level of evidence of the literature
Not applicable.

Summary of international guidelines and consensus documents
European Society of Endocrinology Clinical Practice Guideline
The European Society of Endocrinology (ESE) published a practice guideline in collaboration with the European Network for the Study of Adrenal Tumors (ENSAT) on the management of adrenocortical carcinoma in adults (Fassnacht, 2018). For development of this guideline, a multidisciplinary working group was established. The working group consisted of endocrinologists, oncologists, pathologist and an endocrine surgeon. The guideline used Grading of Recommendations Assessment, Development and Evaluation (GRADE) as a methodological base. Clinical questions regarding pathology, diagnosis and prognostic markers were formed.

The working group of the practice guideline on the management of adrenocortical carcinoma in adults recommends that the pathology report of a (suspected) adrenocortical carcinoma (ACC) should at least contain the following information:

- Weiss score (including the exact mitotic count) (Weiss, 1984; Weiss 1998)
- Exact Ki67 Index
- Resection status
- Pathological tumor stage (indicating invasion or not of the capsule and/or surrounding tissue and organs)
- Nodal stage

International Collaboration on Cancer Reporting for Adrenal Cortical Carcinoma

The International Collaboration on Cancer Reporting (ICCR) compiled a 12-member Dataset Authoring Committee (DAC) to critically review the published evidence and develop a draft data set for Adrenal Cortical Carcinoma (ACC) (Giordano, 2021). The data set includes 23 core elements which are defined as those that are essential for the clinical management, staging, or prognosis of ACC and 9 noncore elements (table 1)

Table 5: Core and Noncore elements for the pathology reporting of ACC

Core	Noncore
Clinical information	Tumor dimensions (additional dimensions)
Operative procedure	Necrosis (extent of necrosis)
Specimen(s) submitted	Reticulin framework
Tumor site	Multifactorial scoring systems
Specimen integrity	Distance of the tumor to the closest margin
Tumor dimensions	Lymph node status (Extranodal extension)
Tumor weight	Coexistent pathology
Histological tumor type	Ancillary studies
Extent of invasion	
Tumor architecture	
Lipid-rich cells	
Capsular invasion	
Lymphatic invasion	
Vascular invasion	
Atypical mitotic figures	
Necrosis (presence or absence)	
Nuclear grade	
Mitotic count and histological tumor grade	
Ki-67 proliferation index	
Margin status (presence of R0, R1 or R2)	
Lymph node status	
Histologically confirmed distant metastases	
Pathological staging	

International Collaboration on Cancer Reporting for Pheochromocytoma and Paraganglioma

The International Collaboration on Cancer Reporting (ICCR) compiled an 11-member Dataset Authoring Committee (DAC) to critically review the published evidence and develop a draft data set for pheochromocytoma and paraganglioma (Thompson, 2021). This data set includes 16 core elements which considered to be the minimum reporting requirements for pheochromocytoma and paraganglioma (PPGL) and five noncore elements (table 2).

Table 6: Core and Noncore elements for the pathology reporting of pheochromocytoma and paraganglioma

Core	Noncore
Clinical information	Tumor dimensions (additional dimensions)
Operative procedure	Margin status
Specimen(s) submitted	• Distance of the tumor to the closest margin
Tumor focality	• Closest margin, specify if possible
Tumor site	Lymph node status (Extranodal extension)
Specimen integrity	Adverse features
Tumor dimensions	Ancillary studies
Medullary hyperplasia	
Histological tumor type	
Extent of invasion	
Lymphovascular invasion	
Margin status	
Proliferative fraction	
Lymph node status	
Histologically confirmed distant metastases	
Pathological staging	

Overwegingen – van bewijs naar aanbeveling

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

Om deze uitgangsvraag te beantwoorden is er geen systematische search gedaan van de literatuur. Er zijn dan ook geen uitkomstmaten benoemd en de literatuur is niet gegradeerd. Internationale richtlijnen en consensus documenten zijn gebruikt om een overzicht te geven van essentiële elementen voor het pathologie verslag (Fassnacht, 2018; Giordano, 2021, Thompson, 2021).

Zowel de internationale richtlijn als het consensus document geven aan dat elementen voor evaluatie van het ACC volgens de Weiss score, Ki67 Index, tumor stadium en lymfklier stadium, tenminste onderdeel moeten zijn van het pathologisch verslag. Opgemerkt moet worden dat de Weiss score internationaal van toepassing wordt geacht op het meest voorkomende type bijnierschorscarcinoom bij volwassen patiënten. Voor oncocytaire tumoren en ACC bij kinderen worden aangepaste systemen gebruikt, die identieke criteria gebruiken, maar met een andere weging. Deze overwegingen zijn beschreven in Giordano (2021). De ICCR dataset heeft alleen individuele pathologische kenmerken als core items en beschouwt multifactoriële scoring systemen als non-core items.

Voor PPGL geldt dat de gepubliceerde multifactoriële scoringssystemen zoals de Pheochromocytoma of the Adrenal gland Scaled Score (PASS) en de Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) eveneens gebaseerd zijn op bepaalde core elements volgens ICCR, maar op zich als non-core element worden beschouwd, overeenkomstig de nieuwe WHO 5^{e} editie over endocriene en neuroendocriene tumoren (Kimura, 2014; Thompson, 2002).

Waarden en voorkeuren van patiënten (en evt. hun wettelijke vertegenwoordigers)
Het verrichten van pathologisch onderzoek op verkregen weefsel wordt doorgaans besproken met de patiënt en in theorie is opt-out mogelijk. Uitslagen worden na de ingreep met de patiënt besproken.

Kosten (middelenbeslag)
Pathologisch onderzoek levert in een hoog percentage van de gevallen een diagnose met hoge betrouwbaarheid op en is relatief goedkoop in vergelijking met de meeste andere klinische en diagnostische onderzoeken. Bekostiging is integraal in de context van diagnose-behandel combinaties, hetgeen de transparantie omtrent de kosten voor individuele onderdelen van het diagnostisch en behandelproces beperkt. Voor ACC wordt op indicatie een biopt genomen, later gevolgd door resectie, indien chirurgisch haalbaar. Bij beide ingrepen wordt aanvullend immuunhistochemisch onderzoek gedaan. In bovengenoemde datasets is moleculair onderzoek niet vereist. Deze verrichtingen vallen in zwaarte categorie 5 en 6 volgens de NZA tabel over normtijden. Er is geen onderzoek bekend naar de kosten/baten analyse van pathologische onderzoek in het algemeen of naar dit tumortype specifiek.

Aanvaardbaarheid, haalbaarheid en implementatie
In Nederland, waar de zorg voor patiënten met bijniertumoren al in belangrijke mate gecentraliseerd is, zijn er in de pathologie geen technische beperkingen voor de implementatie van richtlijn op basis van genoemde publicaties met core of noncore elementen. Op het gebied van de immuunhistochemie komen steeds meer markers beschikbaar, waarvan sommige niet universeel beschikbaar zijn, zoals SF1, GATA3, SDHA en SDHB. Deze behoren echter geen van allen tot de core elementen en zijn overigens gemakkelijk via intercollegiale consultatie beschikbaar.

Aanbevelingen
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Door de zeldzaamheid van ACC zijn er weinig studies in voldoende grote cohorten die de betekenis van histologische en immuunhistochemische kenmerken voor de diagnostiek en prognose van deze tumoren hebben onderzocht. Recent heeft een grote groep internationale pathologen met uitgebreide ervaring en op initiatief van de International Collaboration on Cancer Reporting een dataset samengesteld voor de pathologische rapportage van ACC. Deze is tot stand gekomen op basis van de bestaande literatuur en in belangrijke mate door expert opinion.

Gebruik bij rapportage van biopten van bijnierschorscarcinomen en bij resectie van feochromocytomen en bijnierschorscarcinomen de core elementen uit de ICCR dataset als richtlijn voor pathologische verslaglegging.
- Bij resecties dienen in principe alle items gerapporteerd te worden
- Bij biopten worden alleen die items gerapporteerd die op basis van de beschikbare informatie kunnen worden gegeven

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
In een groot deel van de literatuur wordt de Weiss score aanbevolen en gebruikt voor het onderscheid tussen benigne en maligne bijnierschorstumoren. De reikwijdte van deze score is echter beperkt tot een subgroep van bijnierschorstumoren, vanwege het risico op overdiagnostiek van ACC bij oncocytaire bijnierschorstumoren en bij bijnierschorstumoren bij kinderen. Dit wordt internationaal ook geaccepteerd, zoals aangegeven in de geciteerde literatuur. Opnieuw berust deze aanbeveling op expert opinion.

Gebruik de Weiss score alleen voor niet-oncocytaire ACC bij volwassenen. Voor oncocytaire ACC dient de Lin-Weiss-Bisceglia classificatie gebruikt te worden en voor pediatrische ACC dient vooralsnog de Wieneke/AFIP classificatie gebruikt te worden.

Literatuur

Fassnacht M, Dekkers OM, Else T, Baudin E, Berruti A, de Krijger R, Haak HR, Mihai R, Assie G, Terzolo M. European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2018 Oct 1;179(4):G1-G46. doi: 10.1530/EJE-18-0608. PMID: 30299884.

Giordano TJ, Berney D, de Krijger RR, Erickson L, Fassnacht M, Mete O, Papathomas T, Papotti M, Sasano H, Thompson LDR, Volante M, Gill AJ. Data set for reporting of carcinoma of the adrenal cortex: explanations and recommendations of the guidelines from the International Collaboration on Cancer Reporting. Hum Pathol. 2021 Apr;110:50-61. doi: 10.1016/j.humpath.2020.10.001. Epub 2020 Oct 12. PMID: 33058949.

Kimura N, Takayanagi R, Takizawa N, Itagaki E, Katabami T, Kakoi N, Rakugi H, Ikeda Y, Tanabe A, Nigawara T, Ito S, Kimura I, Naruse M; Phaeochromocytoma Study Group in Japan. Pathological grading for predicting metastasis in phaeochromocytoma and paraganglioma. Endocr Relat Cancer. 2014 May 6;21(3):405-14. doi: 10.1530/ERC-13-0494. PMID: 24521857.

Thompson LDR, Gill AJ, Asa SL, Clifton-Bligh RJ, de Krijger RR, Kimura N, Komminoth P, Lack EE, Lenders JWM, Lloyd RV, Papathomas TG, Sadow PM, Tischler AS. Data set for the reporting of pheochromocytoma and paraganglioma: explanations and recommendations of the guidelines from the International Collaboration on Cancer Reporting. Hum Pathol. 2021 Apr;110:83-97. doi: 10.1016/j.humpath.2020.04.012. Epub 2020 May 11. PMID: 32407815; PMCID: PMC7655677.

Thompson LD. Pheochromocytoma of the Adrenal gland Scaled Score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. Am J Surg Pathol. 2002 May;26(5):551-66. doi: 10.1097/00000478-200205000-00002. PMID: 11979086.

Bijlagen bij module Pathologieverslag

Evidence tables

Niet van toepassing.

Table of excluded studies

Niet van toepassing.

Literature search strategy

Niet van toepassing.

Module 13 – Radiologieverslag

Uitgangsvraag
Welke vaste onderdelen behoren deel uit te maken van een radiologie verslag voor bijnier incidentalomen?

Inleiding
Voor een optimale diagnose en behandeling van het incidentaloom is het essentieel dat alle relevante aspecten bij het radiologisch onderzoek worden geëvalueerd. Het onderzoek moet vervolgens worden gerapporteerd op basis van erkende definities en op een gestandaardiseerde wijze. Het niet aanhouden van standaard terminologie of aanbevelingen kan leiden tot verwarring onder aanvragend clinici en kan leiden tot verschillend beleid en/of follow-up. De beoordelaar dient dus op de hoogte te zijn van beeldvormende kenmerken die een benigne bijnierlaesie onderscheiden van een maligniteit, teneinde hier adviezen over te kunnen geven in verslag en Multi Disciplinair Overleg (MDO). Uitgegaan wordt van veelal initiële detectie van deze nevenbevinding op CT, derhalve wordt in deze module gekeken naar standaardverslaglegging gebaseerd op CT. Enkele van de opgenomen karakteristieken zullen echter ook van nut kunnen zijn voor detectie op MRI of echografie.

Search and select
An explorative review of the literature was performed to answer the following question:
What are standard items in a radiology report for patients with an adrenal incidentaloma?

P (Patients)	Patients with an adrenal incidentaloma
I (Intervention)	Standardized radiology report
C (Control)	Not applicable
O (Outcomes)	Not applicable

Relevant outcome measures
There were no outcome measures defined regarding this explorative review of the literature.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 12-09-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 82 hits. Studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICO;
- The intervention had to be as defined in the PICO;
- Articles written in English or Dutch

Seventeen studies were initially selected based on title and abstract screening. After reading the full text, fourteen studies were excluded (see the table with reasons for exclusion under the tab Methods). One systematic review was included as well as two studies that were referenced in the systematic review and were separately described because additional information was reported.

Summary of literature

Description of studies

Feeney (2022) performed a systematic review describing the adherence to guidelines for incidental adrenal mass (IAM) evaluation and mechanisms to promote evaluation and clinical management of IAMs. Six studies included in this review reported the effect of recommendations in the imaging reports on the rates of IAMs evaluation. One study reported the referral to an endocrinologist as a positive associating factor with follow up rates (Becker, 2017). One study showed that specific IAM recommendations in the radiology reports were associated with increased overall IAM evaluation (Maher, 2018). The study of **Feeney (2019)** showed that specific terms such as 'indeterminate' versus 'likely benign' or other benign-sounding terminology increased the rate of indicated imaging.
The study of **Wickramarachchi (2016)** which was included in the review of Feeney (2022), performed a retrospective analysis of 74 radiology reports. Out of 69 CT scans evaluated, 15 were noncontrast scans and Hounsfield Units (HU) were reported in eleven scans. Advice for follow-up in the radiology report was provided in 31 reports (42%) and follow-up was more likely to occur (54%) than when no recommendation was offered (21%). Advice for referral to an endocrinologist was followed-up in all three times.

The study of **De Haan (2019)** was also included in the review of Feeney (2019). They performed a retrospective analysis of Dutch radiology reports between 2010 and 2012 from a single hospital. Patient reports with procedural codes for CT abdomen and CT thorax and mentioning of a lesion of the adrenal gland, were selected. Patient reports of patients younger than 18 years, patients with initial presentation on other imaging modalities, patients who were referred from another hospital, patients with recorded complaints possibly indicating adrenal disease at the moment and patients with proven or a history of metastasis, were excluded. The reports were divided into two groups according to the description of the mass: Specific adrenal incidentaloma group (n=604) and non-specific adrenal incidentaloma group (n=508).
Twenty-two different specific terms were found in which 'nodule' was the term most frequently used (55.8%) followed by 'enlargement' (17.3%). Twenty-four nonspecific terms were found in which 'plump' was predominantly used (82.2%) followed by 'prominent' (4%). There was a significant difference between the specific and non-specific group regarding nodule size. There were more patients with an adrenal incidentaloma of more than two centimeters in the specific group. Patients in the specific group received significantly more diagnostic workup than patients in the non-specific group.

Results

No outcome measures were defined regarding this explorative review of the literature.

Level of evidence of the literature

Since there were no outcome measures defined, this is not applicable.

Conclusions

No GRADE	Because of the explorative nature of this search no GRADE assessment was performed.

Overwegingen – van bewijs naar aanbeveling

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

De systematische search resulteerde in één systematic review (Feeney, 2022) en twee observationele studies die ook in de systematic review geïncludeerd waren (de Haan, 2019; Wickramarachchi, 2016). Gezien het uitgangspunt van deze vraag en de vraagstelling is er een

PICO opgesteld zonder definitie van controle groep of uitkomstmaten. Er is dan ook geen GRADE beoordeling gedaan.

De huidige studies geven aan dat de mate van opvolgen van de bestaande richtlijnen, gebaseerd op het adequaat verrichten van follow-up beeldvorming en/of lab evaluaties, laag is. De geïncludeerde studies beschrijven dat het gebruik van specifieke terminologie in het radiologie verslag, meest consistent zorgt voor een betere follow-up van het bijnier incidentaloom. Als naar de endocrinoloog wordt verwezen, resulteert dat meestal in adequate follow-up.

Bijnier incidentalomen worden gedetecteerd in ongeveer 1-2% van alle abdominale CT scans, dit percentage neemt toe met de leeftijd van patiënt. Hoewel benigne non-functionerende adenomen het meest voorkomen, ligt de kans om een klinisch relevante bijnierlaesie te ontdekken rond de 25% (Feeney, 2022). Zowel onnodig vervolgen als ten onrechte niet evalueren heeft gevolgen voor de patiënt. Gezien het eerste detectiemoment van een adrenaal incidentaloom is er voor de radiologie een sleutelmoment weggelegd voor een juiste evaluatie en aansturen van vervolg beleid. Adherentie aan richtlijnen kan beeldvormende follow-up als ook biochemisch onderzoek betekenen. Zoals bekend kunnen sommige incidentalomen op de index scan al benoemd worden als benigne (bijvoorbeeld op basis van HU-waarde <10). Ook het juist uitsluiten van maligne kenmerken en het met hoge zekerheid aangeven van een benigne (vethoudend) adenoom kent een zeer belangrijke functie, namelijk het voorkomen van onnodige follow-up. Gezien het voorkomen van het incidentaloom is het relevant dat accuraat benoemd wordt in welke gevallen er geen beeldvormende follow-up of verwijzing nodig is. Dit leidt tot minder belasting van de patiënt alsmede lagere zorgkosten en eventuele stralingsbelasting. Daarentegen is het belangrijk de juiste follow-up, bijvoorbeeld meer-fase contrast CT, te kiezen wanneer men twijfelt over de entiteit op basis van de index scan. De specifieke terminologie om het bijnier incidentaloom te beschrijven omvat termen zoals ‘nodus’, ‘adenoom’ en ‘laesie’. Daarnaast zorgt een term zoals ‘aspecifiek’ ten opzichte van goedaardig lijkende termen zoals ‘waarschijnlijk goedaardig’ voor toename van bijnier specifieke beeldvorming. De Haan (2019) benoemen dat meer specifieke terminologie zorgt voor verbeterde follow-up in zowel beeldvorming als biochemisch onderzoek. Interessant genoeg speelt ook de klinische setting een rol: Bij verwijzingen vanuit de polikliniek is de kans kleiner dat vervolgonderzoek wordt verricht, dan wanneer verwezen wordt vanuit de klinische setting inclusief spoedzorg (Feeney, 2018). Implementatie van een gestandaardiseerd klinisch algoritme (Eldeiry, 2018) leidt tot significante toename van biochemisch onderzoek en follow-up scans. Karakteristieken opgenomen in dit algoritme waren de grootte en beeldvormende kenmerken als HU-waarde, homogeniciteit, begrenzingen en eventuele necrose. Bij een evidente radiologische diagnose cyste of myelolipoom werd hormonale evaluatie afgeraden (Eldeiry, 2018).

Een mogelijke mate van (on)zekerheid over radiologische gegevens kan worden uitgedrukt in een numerieke schatting (Panicek, 2016), hetgeen kan helpen in bepalen van follow-up voor de aanvrager. Daarnaast verbetert het de communicatie tussen aanvragers en radiologisch verslagleggers.

Een mogelijkheid om navolging van de richtlijnen te vergroten zou introductie van standaardverslaglegging kunnen zijn, die is gebaseerd op macro rapporten en adequate bijscholing. Meer studies dienen echter te worden verricht in het nagaan waarom veel incidentalomen niet adequaat worden vervolgd en welke strategieën het meest nuttig zouden zijn om de initiële zorg rond bijnier incidentalomen te verbeteren. Studies met relevante eindpunten op dit vlak zijn echter nog zeldzaam.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Ten aanzien van aanbevelingen in een radiologisch verslag (overwegingen tot follow-up scan en/of verwijzingen) moet worden opgemerkt dat ook de patiënt dergelijke conclusies kan inzien en volgens 'samen beslissen' invloed kan uitoefenen op de vorm van follow-up. Heldere en gestandaardiseerde taal vergroot de transparantie voor patiënten en daarmee de participatie aan hun eigen zorgproces.

Kosten (middelenbeslag)
De overgang naar standaard verslaglegging over dergelijke incidentalomen kan moeilijk objectief in kosten worden uitgedrukt. Voorstelbaar is dat wanneer meer ervaring is opgebouwd met dergelijke verslaglegging, sneller gerapporteerd kan worden en dat communicatie met de clinicus ook duidelijker verloopt. Het adequaat radiologisch uitsluiten van maligne kenmerken van het incidentaloom en vermelden van de grootte (laesies <1 cm) voorkomt naar verwachting onnodige follow-up en kan zorgkosten verlagen (geen extra scan of biochemisch onderzoek nodig). Daarentegen zal accurate terminologie en betere risicostratificatie ook leiden tot toename van het aantal incidentalomen dat wel in aanmerking komt voor verdere follow-up. Meer onderzoek zal derhalve nodig zijn naar kosteneffectiviteit van deze strategieën om duidelijk te krijgen hoe deze balans zich verhoudt.

Aanvaardbaarheid, haalbaarheid en implementatie
Enkele studies uit de systematic review van Feeney (2022) tonen aan dat radiologen na instructie over de toepassing van een gestandaardiseerd algoritme de adherentie ten aanzien van (inter)nationale richtlijnen verbeteren. Het gebruik van macro templates en het regulier (bij)scholen in herkennen van bepalende CT karakteristieken voor bijnierlaesies zou derhalve kunnen helpen. Deze strategie kent relatief lage kosten en zal afhankelijk zijn van kennis en ervaring van de radioloog. Communicatie hierover binnen een multidisciplinair team kan ondersteunend zijn.

Aanbevelingen
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Op dit moment zijn nog weinig grote studies gedaan over de zinvolheid van adequate follow-up gebaseerd op veranderde radiologische verslaglegging. Wel mag aangenomen worden dat standaardverslaglegging en standaard terminologie in de toekomst beter onderzoek mogelijk maakt. Richtlijnen alleen zijn mogelijk niet genoeg om opvolging hiervan te garanderen. Extra strategieën zoals deze radiologische standaardisering kan helpen de juiste patiënten van juiste follow-up te voorzien. Afmeting (grootte in cm), HU-waarde (<10), goede afgrensbaarheid en afwezigheid van necrose worden hierbij consistent genoemd als parameters ter differentiatie van een maligne laesie (zie module 'Diagnostiek bijnier incidentaloom'. Geef ook eventuele groei of verandering aan, wanneer oude beeldvorming beschikbaar is.
Aangenomen wordt op basis van de in deze module opgenomen studies dat gestandaardiseerde verslaglegging en een specifieke conclusie zal leiden tot betere navolging van de richtlijnen. Een duidelijkere risicostratificatie zal hierbij kunnen leiden tot betere communicatie met aanvragers en betere standaardzorg voor patiënten met een adrenaal incidentaloom. Of een dergelijke strategie ook zal leiden tot lagere zorgkosten, is vanuit huidige bewijskracht onduidelijk.

Gebruik ter beschrijving van het bijnier incidentaloom in het radiologisch (CT-) verslag specifieke en gestandaardiseerde terminologie. Kenmerken als grootte, HU-waarde en

afgrensbaarheid spelen hierin een bepalende rol zoals beschreven in module 'Diagnostiek bijnier incidentaloom'.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Aangezien in studies genoemd wordt dat adequate verwijzing (bijv. naar de endocrinoloog) de follow-up verbetert, kan het opnemen van een zin over een dergelijke verwijzing in de conclusie van het verslag, indien geïndiceerd, navolging van bestaande richtlijnen verbeteren. Het toekennen van een grote waarschijnlijkheid op aanwezigheid van een benigne adenoom, myelolipoom of cyste kan onnodige follow-up voorkomen. Twijfel hierover kan de aanvrager juist op het spoor brengen van verdere adequate follow-up. Gezien de aanbeveling follow-up te staken bij evident benigne afwijkingen, is het belangrijk een dergelijke bevinding te benoemen in het verslag. Het is derhalve zinvol kenmerken die een benigne afwijking hoog waarschijnlijk maken (macroscopisch vet, cyste, calcificaties) expliciet te vermelden. Als initiële detector van de indexlaesie speelt de radioloog hierin een belangrijke rol.

Ken in het radiologieverslag een mate van waarschijnlijkheid op benigne dan wel maligne laesie toe aan het gevonden incidentaloom op de index beeldvorming zodat besloten kan worden of eventueel biochemisch onderzoek, follow-up of verwijzing benodigd is. Geef in het verslag aan welke kenmerken bijdragen aan deze mate van waarschijnlijkheid.

Literatuur

Becker J, Woloszyn J, Bold R, et al. The adrenal incidentaloma: an opportunity to improve patient care. *J Gen Intern Med*. 2017:1–2 Available from http://dx.doi.org/10.1007/s11606-017- 4240- 6.

de Haan RR, Schreuder MJ, Pons E, Visser JJ. Adrenal Incidentaloma and Adherence to International Guidelines for Workup Based on a Retrospective Review of the Type of Language Used in the Radiology Report. J Am Coll Radiol. 2019 Jan;16(1):50-55. doi: 10.1016/j.jacr.2018.08.011. Epub 2018 Sep 22. PMID: 30253931.

Feeney T, Madiedo A, Knapp PE, Gupta A, McAneny D, Drake FT. Incidental Adrenal Masses: Adherence to Guidelines and Methods to Improve Initial Follow-Up: A Systematic Review. J Surg Res. 2022 Jan;269:18-27. doi: 10.1016/j.jss.2021.07.041. Epub 2021 Sep 8. PMID: 34508918.

Feeney T, Talutis S, Janeway M, et al. Evaluation of incidental adrenal masses at a tertiary referral and trauma center. *Surgery [Internet]*. 2020;167:868–875 Available from http://dx.doi.org/10.1016/j.surg.2019.07.034.

Maher DI, Williams E, Grodski S, Serpell JW, Lee JC. Adrenal incidentaloma follow-up is influenced by patient, radiologic, and medical provider factors: a review of 804 cases. *Surgery*. 2018;164:1360–1365 Available from http://dx.doi.org/10.1016/j.surg.2018.07.011.

Wickramarachchi BN, Meyer-Rochow GY, McAnulty K, Conaglen JV, Elston MS. Adherence to adrenal incidentaloma guidelines is influenced by radiology report recommendations: investigation of adrenal incidentalomas. *ANZ J Surg*. 2016;86:483–486 Available from http://dx.doi.org/10.1111/ans.12799.

Eldeiry LS, Alfisher M, Callahan C, Hanna N, Garber J. The impact of an adrenal incidentaloma algorithm on the evaluation of adrenal nodules. *J Clin Transl Endocrinol.* 2018 sept; 13: 39-45

Bijlagen bij module Radiologieverslag

Evidence tables
Niet van toepassing.

Table of excluded studies

Reference	Reason for exclusion
Panicek DM, Hricak H. How Sure Are You, Doctor? A Standardized Lexicon to Describe the Radiologist's Level of Certainty. AJR Am J Roentgenol. 2016 Jul;207(1):2-3. doi: 10.2214/AJR.15.15895. Epub 2016 Apr 11. PMID: 27065212.	Wrong study population: All radiology reports
Talutis SD, Childs E, Goldman AL, Knapp PE, Gupta A, Ferrao C, Feeney T, McAneny D, Drake FT. Strategies to optimize management of incidental radiographic findings in the primary care setting: A mixed methods study. Am J Surg. 2022 Feb;223(2):297-302. doi: 10.1016/j.amjsurg.2021.03.038. Epub 2021 Mar 25. PMID: 33810834.	Wrong scope: Incidentaloma management
Gheorghisan-Galateanu AA, Carsote M, Valea A. Incidentaloma: from general practice to specific endocrine frame. J Pak Med Assoc. 2017 Jun;67(6):917-922. PMID: 28585593.	Wrong scope: General and endocrine approach
Watari J, Vekaria S, Lin Y, Patel M, Kim H, Kang F, Lubitz S, Beninato T, Laird AM. Radiology report language positively influences adrenal incidentaloma guideline adherence. Am J Surg. 2022 Feb;223(2):231-236. doi: 10.1016/j.amjsurg.2021.06.015. Epub 2021 Jun 29. PMID: 34243951.	Wrong scope: Factors influencing referral in patients with adrenal incidentaloma, no factors regarding radiology report.
Canton SP, Dadashzadeh E, Yip L, Forsythe R, Handzel R. Automatic Detection of Thyroid and Adrenal Incidentals Using Radiology Reports and Deep Learning. J Surg Res. 2021 Oct;266:192-200. doi: 10.1016/j.jss.2021.03.060. Epub 2021 May 18. PMID: 34020097.	Wrong population: Trauma patients
Lavallée LT, Knee C, Ross J, Lau JL, Mookerji N, van Walraven C. Derivation and validation of text search algorithms for renal and adrenal lesion identification in radiology text reports. Can Urol Assoc J. 2020 Jun;14(6):E264-E270. doi: 10.5489/cuaj.6105. PMID: 31977309; PMCID: PMC7654667.	Wrong study population: Patients with renal mass, renal cyst and adrenal mass
Domingo J, Soni P, Galal G, Mukhin V, Huang J, Caron S, Xinos S. Natural language processing for detection and reporting of findings requiring follow-up in Ra. Diagnosis. 2022 Volume 9.	Wrong population: Thromboembolic disease
Fisher SB, Habra MA, Chiang YJ, Wu SY, Graham PH, Grubbs EG, Lee JE, Perrier ND. Comparative Performance of the 7th and 8th Editions of the American Joint Committee on Cancer Staging Manual for Adrenocortical Carcinoma. World J Surg. 2020	Wrong scope: ACC staging

Feb;44(2):544-551. doi: 10.1007/s00268-019-05136-2. PMID: 31493191.	
Brady A. Incidentalomas, SPEW, and VOMIT-radiological dyspepsia? Eur Radiol. 2020 Sep;30(9):4968-4973. doi: 10.1007/s00330-020-06844-3. Epub 2020 Apr 29. PMID: 32350659.	Wrong population: All incidental findings
Bala W, Steinkamp J, Feeney T, Gupta A, Sharma A, Kantrowitz J, Cordella N, Moses J, Drake FT. A Web Application for Adrenal Incidentaloma Identification, Tracking, and Management Using Machine Learning. Appl Clin Inform. 2020 Aug;11(4):606-616. doi: 10.1055/s-0040-1715892. Epub 2020 Sep 16. PMID: 32937677; PMCID: PMC7542219.	Wrong scope: Algorithm to predict new adrenal incidentaloma on radiology report, no metion of specific factors
Yip SM, Kwok SY. Impact of adrenal incidentaloma in preoperative staging on the management of colorectal cancer. Surg Practice. 2019 Volume 23.	Wrong scope: Management preoperative staging in colorectal cancer and impact AI
Schieda N, Davenport MS, Pedrosa I, Shinagare A, Chandarana H, Curci N, Doshi A, Israel G, Remer E, Wang J, Silverman SG. Renal and adrenal masses containing fat at MRI: Proposed nomenclature by the society of abdominal radiology disease-focused panel on renal cell carcinoma. J Magn Reson Imaging. 2019 Apr;49(4):917-926. doi: 10.1002/jmri.26542. Epub 2019 Jan 28. PMID: 30693607; PMCID: PMC6980339.	Wrong scope: Description of fat in adrenal masses
Eldeiry LS, Alfisher MM, Callahan CF, Hanna NN, Garber JR. The impact of an adrenal incidentaloma algorithm on the evaluation of adrenal nodules. J Clin Transl Endocrinol. 2018 Jul 5;13:39-45. doi: 10.1016/j.jcte.2018.07.001. PMID: 29998066; PMCID: PMC6037878.	Wrong scope: Rates of hormone testing and FU imaging in reports containing algorithm versus no algorithm
McLoud TC. Massachusetts General Hospital experience with structural reporting. Canc Img. 2016 Volume 16.	Wrong scope: Description of all reports in single hospital

Literature search strategy

Algemene informatie

Richtlijn: NVVH- bijniertumoren	
Uitgangsvraag: Welke vaste onderdelen behoren deel uit te maken van een radiologie verslag voor incidentalomen	
Database(s): Ovid/Medline, Embase	Datum:12-9-2022
Periode: 2015-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: Bijniertumoren EN nomenclatuur, verslaglegging Het sleutelartikel wordt gevonden.	

Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 12-9-2022 met relevante zoektermen gezocht naar studies over vaste onderdelen die deel uitmaken van een radiologie verslag over incidentalomen. De literatuurzoekactie leverde 82 unieke treffers op.

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs			
RCTs			
Observationele studies			
Overig	81	19	82
Totaal			

Zoekstrategie

Embase

No.	Query	Results
#5	#4 AND [1-1-2015]/sd	**81**
#4	#2 AND #3	**153**
#3	'nomenclature'/exp OR 'nomenclature':ti,ab,kw OR 'terminology':ti,ab,kw OR (((structur* OR standard*) NEAR/3 (term* OR report*)):ti,ab,kw) OR 'radiology report*':ti,ab,kw	**180583**
#2	'adrenal tumor'/exp OR 'adrenal incidentaloma'/exp OR ((adrenal NEAR/3 (incidental* OR mass* OR lesion* OR tumor* OR cancer OR adenoma* OR nodule*)):ti,ab,kw)	**40288**
#1	adrenal AND incidentaloma AND adherence AND to AND international AND guidelines AND for AND work up AND based AND on AND a AND retrospective AND review AND type AND of AND language AND used A ND in AND the AND radiology	**1**

Ovid/Medline

#	Searches	Results
4	limit 3 to yr="2015 -Current"	19
3	1 and 2	38
2	exp Terminology/ or "Systematized Nomenclature of Medicine"/ or ((structur* or standard*) adj3 (term* or report*)).ti,ab,kf. or 'radiology report*'.ti,ab,kf.	65936
1	Adrenal Gland Neoplasms/ or (adrenal adj3 (incidental* or mass* or lesion* or tumor* or cancer or adenoma* or nodule*)).ti,ab,kf.	31134

Module 14 – Follow-up

Uitgangsvraag
Wat is de optimale duur en frequentie van follow-up voor verschillende typen bijniertumoren (aldosteron producerend adenoom, cortisol producerend adenoom en sporadisch feochromocytoom)?

De uitgangsvraag omvat de volgende deelvragen:
1. Wat is de optimale duur en frequentie van follow-up?
2. Wat is de recidief kans over tijd voor een aldosteron producerend adenoom, cortisol producerend adenoom en sporadisch feochromocytoom?

Inleiding
Er wordt bij verschillende type bijniertumoren (aldosteron producerend adenoom, cortisol producerend adenoom en sporadisch feochromocytoom) vaak lang gecontroleerd na afronding van de behandeling (operatie en reguliere nacontroles/behandeling). Deze controles zijn er onder andere op gericht om een recidief op te sporen. Het is onduidelijk wat de optimale duur is van de follow-up per type bijniertumor. Enerzijds is het van belang om recidieven zo snel mogelijk op te kunnen sporen, anderzijds dient onnodig (lange) follow-up zo veel mogelijk voorkomen te worden.

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

1: What is the effect of follow-up compared with no follow-up or follow-up on indication on overall survival, disease-free survival or quality of life in patients treated for adrenal tumors or sporadic adrenal pheochromocytoma?

P (Patients)	Patients treated for adrenal tumors or sporadic adrenal pheochromocytoma
I (Intervention)	Follow-up
C (Control)	No follow-up or follow-up on indication
O (Outcomes)	Overall survival, disease-free survival, quality of life

2: What are the recurrence rates or time to recurrence in patients treated for adrenal tumors or sporadic adrenal pheochromocytoma?

P (Patients)	Patients treated for adrenal tumors or sporadic pheochromocytoma
O (Outcomes)	Recurrence rate, time to recurrence

<u>Relevant outcome measures</u>
The guideline development group considered overall survival, disease-free survival and quality of life as a critical outcome measure for decision making and recurrence rate and time to recurrence as an important outcome measure 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 the following differences per outcome as a minimal clinically (patient) important difference:

- Overall survival: > 5% or > 3% and Hazard Ratio (HR) < 0.7 (BOM, 2018)
- Disease-free survival: HR < 0.7 (BOM, 2018)
- Quality of life: ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 06-12-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 108 hits. Studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICO's;
- The intervention and comparison had to be as defined in the PICO or reported at least one of the outcomes as defined in the PICO's;
- Research type: Systematic review;
- Full text available;
- Articles written in English or Dutch

Sixteen studies were initially selected based on title and abstract screening. After reading the full text, fourteen studies were excluded (see the table with reasons for exclusion under the tab Methods), and two studies were included.

Results
Two 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
Holscher (2021) performed a systematic review and meta-analysis evaluating the recurrence rate and time to recurrence of sporadic pheochromocytomas after resection. Studies were included in the systematic review when they examined follow-up duration, recurrence rate and time to recurrence after adrenalectomy for primary benign or malignant sporadic adrenal pheochromocytomas. The studies had to report a minimum follow-up duration of two years and a minimum of 10 patients with sporadic pheochromocytoma had to be included in the study. Studies with inclusion period before 1990, case reports and case series, were excluded. In total thirteen studies were included in the data synthesis with a total of 430 patients (Brunt, 2001; Carter, 2012; Castilho, 2009; de Wailly, 2012; Guerrieri, 2005; Inabnet, 2000; Ippolito, 2008; Johnston, 2015; Majtan, 2017; Press, 2014; Tiberio, 2008; Toniato, 2007; Zografos, 2011). In only three studies the cohort exclusively consisted of patients with sporadic pheochromocytoma (Ippolito, 2008; Tiberio, 2008; Inabnet, 2000). Eight studies also included patients with familial pheochromocytomas (Brunt, 2001; Carter, 2012; Castilho, 2009; de Wailly, 2012; Guerrieri, 2005; Press, 2014; Toniato, 2007; Zografos, 2011) and two studies also included paragangliomas (Johnston, 2015; Majtan, 2017). Holscher (2021) reported recurrence and time to recurrence.

Amar (2016) performed a systematic review and meta-analysis to review the incidence of local or metastatic recurrence or new tumors in patients who have undergone complete resection of a non-metastatic pheochromocytoma or thoraco-abdomino-pelvic paraganglioma. Studies were included in the systematic review when they enrolled a minimum of twenty patients who had undergone complete tumor resection, postoperative follow-up was at least one month and the number of patients with tumor recurrence or a

new tumor could be identified. In total 42 studies were included corresponding to 38 cohorts. Only studies who included less than 60% patients with a genetic tumor, were included in our analyses (Agarwal, 2012; Amar, 2005; Amar, 2006; Beatty, 1996; Cotesta, 2009; Edström Elder, 2003; Favia, 1998; Geoghegan, 1998; Grozinsky-Glasberg, 2010; Van der Harst, 2002; Hayry, 2009; Iacobone, 2011; Jaroszewski, 2003; Kercher, 2002; Khorram-Manesh, 2005; Zhang, 2007; Lang, 2008; Lucon, 1997; Lumachi, 1998; Noshiro, 2000; Obara, 1995; Pan, 2005; Park, 2011; Pomares, 1998; Scott, 1984; Stenström, 1988; Timmers, 2008; Tormey, 2002; Wilhelm, 2006). Mean or median duration of follow-up was between six and 192 months.
Amar (2016) reported recurrent disease (same-site, other site and metastases).

Results
Overall survival
None of the included systematic reviews reported overall survival.

Disease-free survival
None of the included systematic reviews reported disease-free survival.

Quality of life
None of the included systematic reviews reported quality of life.

Recurrence rate
Two systematic reviews reported recurrence rate (Holscher, 2021; Amar, 2016).
An overview of the individual studies included in the systematic reviews, study population, follow-up duration and recurrence rate are presented in **Table 1**.

Table 7. Recurrence rates

Study	Study population	Number of patients	Follow-up duration (months)	Number of events	Recurrence rate (95%CI)
Agarwal (2012)	Patients with pheochromocytoma or paraganglioma	101	Mean 44	1	0.01 (NR)
Amar (2005) (2006)	Patients with pheochromocytoma (21% familial) or paraganglioma	261	Mean 102	36	0.14 (NR)
Beatty (1996)	Patients with pheochromocytoma (24% familial) or paraganglioma	41	NR	6	0.15 (NR)
Brunt (2001)	Patients with sporadic or familial pheochromocytoma	15	Mean 46	0	0.00 (0.00-0.22)
Carter (2012)	Patients with sporadic or familial pheochromocytoma	20	Mean 53	0	0.00 (0.00-0.17)
Castilho (2009)	Patients with sporadic or familial pheochromocytoma	21	Mean 70.2	0	0.00 (0.00-0.16)
Costeta (2009)	Patients with pheochromocytoma (23% familial) or paraganglioma	91	Range 6-192	3	0.03 (NR)
De Wailly (2012)	Patients with sporadic or familial pheochromocytoma	40	Mean 84	1	0.02 (0.00-0.13)
Edström Elder (2003) (2003)	Patients with pheochromocytoma (18% familial) or paraganglioma	85	Median 144	5	0.06 (NR)
Favia (1998)	Patients with pheochromocytoma (7% familial) or paraganglioma	55	Mean 88	2	0.04 (NR)

Study	Study population	Number of patients	Follow-up duration (months)	Number of events	Recurrence rate (95%CI)
Geoghegan (1998)	Patients with pheochromocytoma (28% familial) or paraganglioma	43	Mean 31	0	0.00 (NR)
Grozinsky-Glasberg (2010)	Patients with pheochromocytoma or paraganglioma	43	NR	0	0.00 (NR)
Guerrieri (2005)	Patients with sporadic or familial pheochromocytoma	14	Mean 48	0	0.00 (0.00-0.23)
Hayry (2009)	Patients with pheochromocytoma or paraganglioma	42	Mean 103	4	0.10 (NR)
Iacobone (2011)	Patients with pheochromocytoma (24% familial) or paraganglioma	71	Median 126	3	0.04 (NR)
Inabnet (2000)	Patients with sporadic pheochromocytoma	22	Mean 44.5	0	0.00 (0.00-0.15)
Ippolito (2008)	Patients with sporadic pheochromocytoma	17	Mean 63.5	0	0.00 (0.00-0.20)
Jaroszewski (2003)	Patients with pheochromocytoma (13% familial) or paraganglioma	47	Mean 41	1	0.02 (NR)
Johnston (2015)	Patients with sporadic or familial pheochromocytoma or paraganglioma	35	Mean 100.5	1	0.03 (0.00-0.15)
Kercher (2002)	Patients with pheochromocytoma (10% familial) or paraganglioma	39	Mean 14	0	0.00 (NR)
Khorram-Manesh (2005)	Patients with pheochromocytoma (25% familial) or paraganglioma	121	Mean 180	9	0.07 (NR)
Majtan (2017)	Patients with sporadic or familial pheochromocytoma or paraganglioma	41	Mean 61.2	0	0.00 (0.00-0.09)
Zhang (2007) Lang (2008)	Patients with pheochromocytoma or paraganglioma	103	Range 5-36	0	0.00 (NR)
Lucon (1997)	Patients with pheochromocytoma (12% familial) or paraganglioma	50	Mean 33	0	0.00 (NR)
Lumachi (1998)	Patients with pheochromocytoma (7% familial) or paraganglioma	55	Mean 88.2	1	0.02 (NR)
Noshiro (2000)	Patients with pheochromocytoma (15% familial) or paraganglioma	95	Mean 117	8	0.08 (NR)
Obara (1995)	Patients with pheochromocytoma (14% familial) or paraganglioma	87	Median 58	4	0.05 (NR)
Pan (2005)	Patients with pheochromocytoma or paraganglioma	26	Median 66	0	0.00 (NR)
Park (2011)	Patients with pheochromocytoma (2% familial) or paraganglioma	152	Mean 41.5	12	0.08 (NR)
Pomares (1998)	Patients with pheochromocytoma (52% familial) or paraganglioma	44	Mean 96	1	0.02 (NR)
Press (2014)	Patients with sporadic or familial pheochromocytoma	117	Mean 87.5	6	0.05 (0.02-0.11)

Study	Study population	Number of patients	Follow-up duration (months)	Number of events	Recurrence rate (95%CI)
Scott (1984)	Patients with pheochromocytoma (12% familial) or paraganglioma	69	Mean 103	5	0.07 (NR)
Stenström (1988)	Patients with pheochromocytoma (20% familial) or paraganglioma	64	Mean 139.2	4	0.06 (NR)
Tiberio (2008)	Patients with sporadic pheochromocytoma	22	Mean 35	0	0.00 (0.00-0.15)
Timmers (2008)	Patients with pheochromocytoma (20% familial) or paraganglioma	69	Mean 132	9	0.13 (NR)
Toniato (2007)	Patients with sporadic or familial pheochromocytoma	41	Mean 102	0	0.00 (0.00-0.09)
Tormey (2002)	Patients with pheochromocytoma (59% familial) or paraganglioma	39	NR	5	0.13 (NR)
Wilhelm (2006)	Patients with pheochromocytoma (14% familial) or paraganglioma	65	Mean 24	1	0.02 (NR)
Zografos (2011)	Patients with sporadic or familial pheochromocytoma	25	108	0	0.00 (0.00-0.14)
NR: Not reported					

Time to recurrence

Three studies in the systematic review of Holscher (2021) reported time to recurrence (de Wailly, 2012; Johnston, 2015; Press, 2014). Results are presented in **Table 2**.

Table 8. Time to recurrence

Study	Number of recurrences	Time until recurrence (in months)
De Wailly, 2012	1	41
Johnston, 2015	1	144
Press	6	7-106

Level of evidence of the literature

The level of evidence of observational cohort studies is considered low according to the GRADE methodology. Therefore, the level of evidence of these cohort studies starts at low GRADE.

The level of evidence regarding the outcome measure **recurrence rate** was downgraded by three levels because of study limitations (-1; risk of bias), applicability (-1; bias due to indirectness because the population included in the studies is partially corresponding with the population as defined in the PICO) and number of included patients (-1; imprecision because of small number of events). Therefore the evidence was graded as very low.

The level of evidence regarding the outcome measure **time to recurrence** was downgraded by two levels because of study limitations (risk of bias), applicability (-1; bias due to indirectness because the population included in the studies is partially corresponding with the population as defined in the PICO) and number of included patients (-1; imprecision because of small sample size). Therefore the evidence was graded as very low.

Conclusions

No GRADE	No evidence was found regarding the effect of follow-up on **overall survival** in patients treated for adrenal tumors or sporadic adrenal pheochromocytoma. *Source: -*

No GRADE	No evidence was found regarding the effect of follow-up on **disease-free survival** in patients treated for adrenal tumors or sporadic adrenal pheochromocytoma. *Source: -*

No GRADE	No evidence was found regarding the effect of follow-up on **quality of life** in patients treated for adrenal tumors or sporadic adrenal pheochromocytoma. *Source: -*

Very low GRADE	The evidence is very uncertain about the **recurrence rates** of patients treated for adrenal tumors or sporadic adrenal pheochromocytoma. *Source: Holscher, 2021; Amar, 2016*

Very low GRADE	The evidence is very uncertain about the **time to recurrence** of patients treated for adrenal tumors or sporadic adrenal pheochromocytoma. *Source: Holscher, 2021*

Overwegingen – van bewijs naar aanbeveling

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

Voor de drie cruciale uitkomstmaten (algehele overleving, ziektevrije overleving en kwaliteit van leven) zijn geen uitkomsten gerapporteerd.
Er zijn twee systematic reviews die voor de belangrijke uitkomstmaten (recurrence rate en tijd tot recurrence) uitkomsten hebben gerapporteerd (Holscher, 2021; Amar, 2016).

De systematic review van Holscher (2021) heeft gekeken naar de recurrence rate en tijd tot recurrence na resectie van patiënten met een sporadisch feochromocytoom, genetisch feochromocytoom of paraganglioom.

De systematic review van Amar (2016) heeft gekeken naar de recurrence rate na resectie van patiënten met een feochromocytoom of paraganglioom. Uit deze systematic review zijn alleen studies meegenomen waarbij minder dan 60 procent van de geïncludeerde patiënten een genetisch feochromocytoom had. Daarbij wordt niet vermeld welke genetische oorzaken zijn onderzocht of welk genetische diagnoses zijn gesteld.
Vanwege de heterogeniteit in de studie populaties, zijn de recurrence rates niet gepoold. Over het algemeen zijn de gerapporteerde recurrence rates laag. In de systematic review van Holscher (2021) is gekeken naar tijd tot recurrence waarbij dit door drie studies gerapporteerd is. De range van tijd tot recurrence varieerde van 6 tot 144 maanden.

De geïncludeerde studies in de systematic reviews waren, op één na, allemaal observationele cohort studies. Er is daardoor een zeer lage bewijskracht. Ook omdat de studie populaties uit

de geïncludeerde studies maar gedeeltelijk overeenkomen met de patiëntpopulatie zoals in deze module beschreven (patiënten met verschillende type bijniertumoren). Resultaten uit de geïncludeerde systematic reviews (patiënten met een (sporadisch) feochromocytoom of paraganglioom) kunnen dus niet één-op-één overgenomen worden voor andere type bijniertumoren.

De studie van Li (2023) is na de zoekdatum gepubliceerd en daarom niet geïncludeerd in bovenstaande literatuursamenvatting. Li (2023) heeft een retrospectieve analyse gedaan bij 398 patiënten met een sporadisch (n=224) of genetisch feochromocytoom (n=174). De studie van Li (2023) concludeert dat in 14.7 procent van de patiënten met sporadisch feochromocytoom, recurrence optreedt door onder andere metastasering van de ziekte. Bij een gedeelte van de patiënten keert de ziekte binnen vijf jaar terug (34.2%), bij een deel binnen 10 jaar (29.1%) en zelfs na 15 jaar (17.7%). Li (2023) geeft hierbij aan dat dit een indicatie kan zijn voor langdurige follow-up bij deze patiënten.

Beleid bij cortisol producerende tumoren en bescherming tegen postoperatieve bijnierschorsinsufficiëntie

Er is een peri- en postoperatief glucocorticoïdstressschema bij patiënten waarbij bijnierschorsinsufficiëntie postoperatief verwacht wordt (zie module ‘Aandacht bijnierschorsinsufficiëntie’). Het glucocorticoïd stresschema wordt afgebouwd en omgezet naar een substitutietherapie met hydrocortison en (alleen bij primaire bijnierschorsinsufficiëntie) fludrocortison volgens de daarvoor geldende richtlijnen (Fassnacht, 2023; Nieman, 2015).

Voor patiënten met het (subklinisch) syndroom van Cushing gebeurt het afbouwen van de hydrocortison geleidelijk op basis van de klachten. De hydrocortison kan worden gestopt als de hypofyse-bijnier as volledig is hersteld, afgelezen aan een ochtend cortisol waarde of een ACTH stimulatietest. Tijdens het afbouwen bestaat een mogelijkheid voor het ontstaan van “glucocorticoid withdrawal syndrome”. Ondanks het gebruik van fysiologische dosering met hydrocortison, hebben veel patiënten last van glucocorticoïdontwenning.

Er zijn specifieke aandachtspunten bij reguliere behandeling:

- Alle patiënten met bijnierschorsinsufficiëntie moeten zelfmanagementvaardigheden ontwikkelen om adequaat te handelen in stresssituaties of bij een (dreigende) bijniercrisis. Het is daarom van belang dat zij en diens naasten voorlichting ontvangen over het toepassen van (orale) dosis verhoging en training in het toedienen van een noodinjectie met hydrocortison ter preventie van een (dreigende) bijniercrisis. De inhoud van deze voorlichting en de uniforme stressinstructies is uitgewerkt in de kwaliteitstandaard bijnieraandoeningen (BijnierNET, 2017).
- Patiënten met syndroom van Cushing kunnen na een curatieve adrenalectomie blijvende klachten ervaren die een negatieve invloed kan hebben op hun kwaliteit van leven. Het is belangrijk om hier aandacht voor te hebben, ondersteuning te bieden en zo nodig door te verwijzen op basis van gesignaleerde problemen.

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

Follow-up kan volgens het principe van gezamenlijke besluitvorming op maat gesneden zijn voor iedere patiënt. Een wetenschappelijke onderbouwing voor controles na afronding van de reguliere behandeling voor patiënten met een aldosteron of cortisol producerende tumor lijkt er niet te zijn.

De follow-up voor patiënten met een feochromocytoom zonder een genetische oorzaak , hoeft wellicht niet levenslang, mits herevaluatie van genetisch testen gewaarborgd is en actualisering overwogen is.

Patiënten die na behandeling bijnierschorsinsufficiënt zijn, blijven onder behandeling van een internist-endocrinoloog. Het is aan te bevelen dat een verpleegkundig specialist, werkzaam binnen de endocrinologie (of een gespecialiseerde endocrinologie verpleegkundige), direct betrokken wordt bij de behandeling en begeleiding van patiënten met bijnierschorsinsufficiëntie. Een van zijn belangrijkste taken is het begeleiden van patiënten in de ontwikkeling van zelfmanagementvaardigheden om met de ziekte om te leren gaan en om adequaat te handelen in stresssituaties of bij een (dreigende) bijniercrisis. Hierbij heeft de verpleegkundig specialist aandacht voor de psychosociale impact van bijnierschorsinsufficiëntie.

Kosten (middelenbeslag)
Langdurige follow-up gaat gepaard met hogere kosten dan een expectatief beleid of ontslag van verdere controles.

Aanvaardbaarheid, haalbaarheid en implementatie
Conform andere richtlijnen is er weinig rationale voor een langdurige follow-up voor patiënten met een aldosteron- of cortisolproducerende tumor (Fassnacht, 2016). Voor de follow up van patiënten met een sporadisch feochromocytoom is geen eenduidig wetenschappelijk bewijs of langdurige follow wel of niet zinvol is (Holscher, 2021; Amar, 2016; Li, 2023). De huidige internationale richtlijnen zijn hierover ook niet eenduidig.
De follow-up van patiënten met een feochromocytoom bestaat uit het jaarlijks meten van plasma metanefrines en aanvullend onderzoek bij afwijkingen. De werkgroep is van mening dat deze follow-up eenvoudig te implementeren is in de praktijk.

Aanbevelingen
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
De literatuur biedt geen tot weinig handreikingen voor een langdurige follow-up van patiënten met aldosteron- of cortisolproducerend bijnieradenoom.

Voor patiënten met een feochromocytoom en een (waarschijnlijk) pathogene variant in een van de nu bekende predispositiegenen wordt levenslange follow-up geadviseerd. Er is momenteel geen methode gebaseerd op pathologisch onderzoek van een sporadische gereseceerde tumor om mogelijke maligniteit of recidief uit te sluiten. Daarom blijft periodieke follow-up op lange termijn aanbevolen voor alle gevallen van feochromocytoom. Genetische tests zullen in toenemende mate de sleutelfactor zijn bij het inschatten van het levenslange risico op de ontwikkeling van terugkerende ziekten, contralaterale aandoeningen of kwaadaardige dedifferentiatie en zo de follow-up protocollen beïnvloeden. Over de duur van deze follow-up is discussie mogelijk. Er zijn goede argumenten om deze follow-up niet levenslang te laten duren, maar na een periode van 10 jaar te evalueren en opnieuw te beslissen. Bij de evaluatie is dan een update van reeds verricht genetisch onderzoek (nieuwe technieken en de identificatie van andere predispositiegenen dan die reeds getest zijn) te overwegen, om daarmee een langere duur van de follow up te onderbouwen. Genetisch onderzoek dient te zijn verricht en indien van toepassing te worden geactualiseerd volgens de dan geldende inzichten. .

Volg patiënten met een **sporadisch aldosteron-** of **cortisol producerend bijnieradenoom** niet langdurig indien postoperatieve hormonale waarden passen bij remissie.

Vervolgbehandeling voor persisterende morbiditeit (bijvoorbeeld hypertensie, diabetes, osteoporose) ondanks biochemische remissie kan nodig zijn.

Evalueer na 10 jaar follow-up bij patiënten met een **sporadisch feochromocytoom** de noodzaak voor verdere periodieke onderzoeken mede in het licht van actuele genetische informatie en genetisch onderzoek.

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Bijlagen bij module Follow-up

Evidence tables

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

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Holscher, 2021 Individual study characteristics deduced from Holscher, 2021	SR and meta-analysis of 13 cohort studies *Literature search up to 2 August 2019* **A**: Brunt, 2001 **B**: Carter, 2012 **C**: Castilho, 2009 **D**: de Wailly, 2012 **E**: Guerrieri, 2005 **F**: Inabnet, 2000 **G**: Ippolito, 2008 **H**: Johnston, 2015 **I**: Majtan, 2017 **J**: Press, 2014 **K**: Tiberio, 2008 **L**: Toniato, 2007 **M**: Zografos, 2011 Study design: Cohort - Prospective: I, K - Retrospective: A, B, C, D, E, F, G, H, J, L, M Setting and Country: Not reported.	Inclusion criteria SR: Studies were eligible for inclusion if they examined the follow-up duration, recurrence rate, and time to recurrence after adrenalectomy for primary benign or malignant sporadic adrenal pheochromocytomas. Minimum reported follow-up duration was 2 years and minimum amount of patients was 10. RCTs, prospective cohort studies and retrospective cohort studies were included. Only publications in English and Dutch were included. Exclusion criteria SR: Studies with an inclusion period before 1990, studies	Describe intervention: No intervention.	Describe control: No control.	End-point of follow-up: Mean follow-up (months): **A:** 46 (2-85) **B**: 53 ± 7 **C**: 70.2 ± 38.7 **D**: 84 **E**: 48 ± 26 **F**: 44.5 (26-72) **G**: 63.5 ± 26.5 **H**: 100.5 ± 71 **I**: 61.2 ± 4.8 **J**: 87.5 ± 27.3 **K**: 35 ± 16.5 **L**: 102 ± 30 **M**: 108 ± 35.5 For how many participants were no complete outcome data available? Not reported.	Recurrence rate Development of tumor recurrence after curative adrenalectomy. **A**: Events: 0, Proportion: 0.00 (95% CI 0.00 to 0.22) **B**: Events: 0, Proportion: 0.00 (95% CI 0.00 to 0.17) **C**: Events: 0, Proportion: 0.00 (95% CI 0.00 to 0.16) **D**: Events: 1, Proportion: 0.02 (95% CI 0.00 to 0.13) **E**: Events: 0, Proportion: 0.00 (95% CI 0.00 to 0.23) **F**: Events: 0, Proportion: 0.00 (95% CI 0.00 to 0.15) **G**: Events: 0, Proportion: 0.00 (95% CI 0.00 to 0.20) **H**: Events: 1, Proportion: 0.03 (95% CI 0.00 to 0.15)	Risk of bias (high, some concerns or low): Not reported in the SR. In only three studies, the cohort exclusively consisted of patients with sporadic pheochromocytomas (F, G, K). Eight studies also included patients with familial pheochromocytomas (A, B, C, D, E, J, L, M), and two studies also included paragangliomas (H, I). Authors conclusion: tumor recurrence rates for truly sporadic pheochromocytomas after curative resection are low. More limited follow-

	Source of funding and conflicts of interest: Source of funding not reported. The authors of the SR have nothing to disclose.	categorizing paragangliomas under pheochromocytomas which did not distinguish between the two types were excluded. *13 studies included* Important patient characteristics at baseline: N, mean age **A**: 15 patients, 42 ± 17 yrs **B**: 20 patients, 54 ± 3 yrs **C**: 21 patients, 46 ± 15.7 yrs **D**: 40 patients, 53 ± 38 yrs **E**: 14 patients, 42 (25-72) yrs **F**: 22 patients, 48.6 ± 12.2 yrs **G**: 17 patients, 48 (25-85) yrs **H**: 35 patients, 55.2 ± 2 yrs **I**: 41 patients, 53.4 ± 12.9 yrs **J**: 117 patients, 51.3 ± 10.8 yrs **K**: 22 patients, 51 ± 10 yrs **L**: 41 patients, 44 ± 13.3 yrs **M**: 25 patients, 54 (19-72) yrs				**I**: Events: 0, Proportion: 0.00 (95% CI 0.00 to 0.09) **J**: Events: 6, Proportion: 0.05 (95% CI 0.02 to 0.11) **K**: Events: 0, Proportion: 0.00 (95% CI 0.00 to 0.15) **L**: Events: 0, Proportion: 0.00 (95% CI 0.00 to 0.09) **M**: Events: 0, Proportion: 0.00 (95% CI 0.00 to 0.14) Pooled effect (random effects model): Proportion 0.03 (95% CI 0.02 to 0.06). Heterogeneity (I^2): 0% Pooled recurrence rate = 3% Time until recurrence (months) **D**: 41 **H**: 144 **J**: 7, 8, 9, 26, 54, 106 WMD: 49.4 months (SD 30.7, range 7-144 months).	up strategies, by means of biochemical testing, for patients with truly sporadic pheochromocytomas could be considered. No GRADE was performed in the systematic review. Sensitivity analysis: Was performed by repeating the meta-analysis and excluding a single study each time. Sensitivity analysis showed the same results.

		None of the included studies used a comparing cohort.					
Amar, 2016 Individual study characteristics deduced from Amar, 2016	SR and meta-analysis of 27 cohort studies * *Literature search from 1 January 1980 up to 19 October 2012* **A:** Agarwal, 2012 **B**: Amar, 2005/2006 **C**: Beatty, 1996 **D**: Costeta, 2009 **E**: Edström Elder, 2003/2003 **F**: Favia, 1998 **G**: Geoghegan, 1998 **H**: Grozinsky-Glasberg, 2010 **I**: Van der Harst, 2002 **J**: Häyry, 2009 **K**: Iacobone, 2011 **L**: Jaroszewski, 2003 **M**: Kercher, 2002 **N**: Khorram-Manesh, 2005 **O**: Zhang, 2007/Lang, 2008 **P**: Lucon, 1997 **Q**: Lumachi, 1998 **R**: Noshiro, 2000 **S**: Obara, 1995 **T**: Pan, 2005 **U**: Park, 2011 **V**: Pomares, 1998 **W**: Scott, 1984 **X**: Stenström, 1988 **Y**: Timmers, 2008 **Z**: Tormey, 2002 **α**: Wilhelm, 2006	Inclusion criteria SR: Studies were eligible if they enrolled at least 20 patients with PH/PG, patients had reportedly undergone complete tumor resection, postoperative follow-up exceeded 1 month, and the number of patients with recurrence or new tumor could be identified. Exclusion criteria SR: - *27 studies included* <u>Important patient characteristics at baseline</u>: <u>N, mean age</u> **A**: 101 patients, 36 ± 14.6 yrs **B**: 261 patients, 42.5 ± 15 yrs **C**: 41 patients, - **D**: 91 patients, 48 (8-77) yrs **E**: 85 patients, 14-77 yrs **F**: 55 patients, median 41 (10-63) yrs **G**: 43 patients, 42 (16-73) yrs **H**: 43 patients, 52.6 (16-77) yrs **I**: 87 patients, 46 (9-78) yrs	Describe intervention: No intervention.	Describe control: No control.	<u>End-point of follow-up</u>: Follow-up duration (months) **A**: mean 44 (3-160) **B**: mean 102 (45.6-158.4) **C**: mean 84 **D**: 6-192 **E**: median 144 **F**: mean 88 (6-232) **G**: mean 31 (9-120) **H**: - **I**: median 120 (3-192) **J**: mean 103 (20-284) **K**: median 126 (6-300) **L**: mean 41 (10-89) **M**: mean 14 (1-40) **N**: mean 180 **O**: 5-36 **P**: mean 33 (0.33-192) **Q**: mean 88.2 (6-232) **R**: mean 117 **S**: median 58 (1-164) **T**: median 66 (24-132) **U**: mean 41.5 (0.9-298) **V**: mean 96 (24-216) **W**: mean 103 (12-348) **X**: mean 139.2 (12-324) **Y**: mean 132 (12-456) **Z**: - **α**: mean 24 (1-84) <u>For how many participants were no complete outcome data available?</u> Not reported.	<u>Same-site recurrences</u> **A**: 0 **B**: 18 **C**: 2 **D**: 2 **E**: 2 **F**: 1 **G**: 0 **H**: 0 **I**: 0 **J**: 1 **K**: 2 **L**: 0 **M**: 0 **N**: 2 **O**: 0 **P**: 0 **Q**: 1 **R**: 1 **S**: 0 **T**: 0 **U**: 0 **V**: 0 **W**: 0 **X**: 0 **Y**: 2 **Z**: 2 **α**: 1 <u>Other-site recurrences</u> **A**: 0 **B**: 0 **C**: 0 **D**: 0 **E**: 0 **F**: 1 **G**: 0 **H**: 0 **I**: 1	* Only studies with <69% genetic tumours were taken into account for our analyses. So, 27/42 studies reported in the SR of Amar (2016) were used for our analyses. <u>Risk of bias (high, some concerns, low):</u> Not reported in the SR. <u>Authors conclusion:</u> risk of recurrent disease following complete resection of a pheochromocytoma or a thoraco-abdomino-pelvic paraganglioma is lower than previously estimated. The risk remains approximately 5% per 5 years of follow-up. Paragangliomas and familial disease are the two main independent risk factors of recurrent disease. No GRADE was performed in the systematic review.

	<u>Study design</u>: All included studies except for X (Stenström, 1988) were retrospective cohort studies. Stenström was a prospective cohort study. <u>Setting (surgical team/medical team) and Country</u>: **A:** Surgery, India **B**: Medicine, France **C**: Mixed, Ireland **D**: Medicine, Italy **E**: Mixed, Sweden **F**: Surgery, Italy **G**: Surgery, UK **H**: Medicine, Israel **I**: Mixed, The Netherlands **J**: Laboratory, Finland **K**: Medicine, Italy **L**: Surgery, USA **M**: Surgery, USA **N**: Medicine, Sweden **O**: Surgery, China **P**: Mixed, Brazil **Q**: Surgery, Italy **R**: Medicine, Japan **S**: Surgery, Japan **T**: Surgery, China **U**: Surgery, Korea **V**: Medicine, Spain **W**: Surgery, USA **X**: Mixed, Sweden **Y**: Medicine, The Netherlands **Z**: Medicine, Ireland	**J**: 42 patients, 46.5 yrs **K**: 71 patients, 44.8 (15-80) yrs **L**: 47 patients, 53.1 (16-81) yrs **M**: 39 patients, 43 (19-59) yrs **N**: 121 patients, 47.2 ± 16.8 yrs **O**: 103 patients, 35.8 ± 13.3 yrs **P**: 50 patients, median 33 (10-64) yrs **Q**: 55 patients, 41 (10-63) yrs **R**: 95 patients, 40 ± 14 yrs **S**: 87 patients, median 40 (11-67) yrs **T**: 26 patients, 39.5 ± 8.9 yrs **U**: 152 patients, 46.5 (18-76) yrs **V**: 44 patients, 43 ± 13.7 yrs **W**: 69 patients, 9-79 yrs **X**: 64 patients, 45 (15-79) yrs **Y**: 69 patients, 46.1 ± 15.6 yrs **Z**: 39 patients, median 36 (8-76) yrs **α**: 65 patients, 48.5 ± 16.1 yrs <u>Sex (% Female)</u>: **A**: 43 **B**: 52 **C**: 54 **D**: 52 **E**: 56 **F**: 49				**J**: 0 **K**: 0 **L**: 1 **M**: 0 **N**: 1 **O**: 0 **P**: 0 **Q**: 0 **R**: 2 **S**: 4 **T**: 0 **U**: 0 **V**: 0 **W**: 0 **X**: 2 **Y**: 0 **Z**: 3 **α**: 0 <u>Metastases</u> **A**: 1 **B**: 18 **C**: 4 **D**: 1 **E**: 3 **F**: 0 **G**: 0 **H**: 0 **I**: 14 **J**: 3 **K**: 1 **L**: 0 **M**: 0 **N**: 6 **O**: 0 **P**: 0 **Q**: 0 **R**: 5 **S**: 0 **T**: 0 **U**: 12 **V**: 1	<u>Sensitivity analysis:</u> Performed based on the availability of the mean duration of follow-up and by risk of bias.

	α: Surgery, USA <u>Source of funding and conflicts of interest:</u> This research was partly funded by the European Society of Endocrinology. The authors declare that there is no conflict of interest.	**G**: 67 **H**: 49 **I**: 55 **J**: - **K**: 52 **L**: 51 **M**: 64 **N**: 56 **O**: 49 **P**: 56 **Q**: 49 **R**: 55 **S**: 56 **T**: 58 **U**: 47 **V**: 54 **W**: 58 **X**: 53 **Y**: 64 **Z**: 38 **α**: 62 <u>Tumor type (% Pheochromocytoma):</u> **A**: 82 **B**: 87 **C**: 84 **D**: 92 **E**: 82 **F**: 91 **G**: 100 **H**: 88 **I**: 89 **J**: 95 **K**: 93 **L**: 100 **M**: 97 **N**: 93 **O**: 100 **P**: 84 **Q**: 90 **R**: -				**W**: 5 **X**: 2 **Y**: 7 **Z**: 0 **α**: 0 <u>Attributable death</u> **A**: 0 **B**: 0 **C**: 4 **D**: 2 **E**: 2 **F**: 0 **G**: 1 **H**: 0 **I**: 10 **J**: 0 **K**: - **L**: 0 **M**: 0 **N**: 4 **O**: 0 **P**: 0 **Q**: 0 **R**: 4 **S**: 1 **T**: 0 **U**: 12 **V**: 0 **W**: 4 **X**: 0 **Y**: 7 **Z**: 2 **α**: 0 <u>Events/100 person-years (95% CI):</u> **A**: 0.27 (0.01 to 1.52) **B**: 1.75 (1.23 to 2.42) **C**: 2.26 (0.83 to 4.91) **D**: - **E**: 0.52 (0.17 to 1.22) **F**: 0.54 (0.07 to 1.97)	

		S: 84 **T**: 85 **U**: 90 **V**: 98 **W**: 77 **X**: 94 **Y**: 88 **Z**: 87 **α**: 100 <u>Genetic diseases (%):</u> **A**: - **B**: 21 **C**: 24 **D**: 23 **E**: 18 **F**: 7 **G**: 28 **H**: - **I**: 31 **J**: - **K**: 24 **L**: 13 **M**: 10 **N**: 25 **O**: - **P**: 12 **Q**: 7 **R**: 15 **S**: 14 **T**: - **U**: 2 **V**: 52 **W**: 12 **X**: 20 **Y**: 20 **Z**: 59 **α**: 14 None of the included studies used a comparing cohort.				**G**: 0.00 (0.00 to 3.48) **H**: - **I**: 1.90 (1.06 to 3.13) **J**: 1.29 (0.35 to 3.31) **K**: 0.37 (0.08 to 1.07) **L**: 0.65 (0.02 to 3.62) **M**: 0.00 (0.00 to 8.02) **N**: 0.50 (0.23 to 0.94) **O**: - **P**: 0.00 (0.00 to 3.84) **Q**: 0.27 (0.01 to 1.51) **R**: 1.11 (0.48 to 2.18) **S**: 0.83 (0.23 to 2.12) **T**: 0.00 (0.00 to 2.46) **U**: 2.36 (1.22 to 4.13) **V**: 0.30 (0.01 to 1.66) **W**: 1.10 (0.36 to 2.56) **X**: 0.54 (0.15 to 1.38) **Y**: 1.28 (0.58 to 2.43) **Z**: - **α**: 1.09 (0.03 to 6.06)	

Risk of bias table

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

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/not applicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Holscher, 2021	Yes	Yes	No, no description of excluded studies (and reason)	Yes	Not applicable	Yes	Yes	No	No
Amar, 2016	Yes	Yes	No, no description of excluded studies (and reason)	Yes	Not applicable	Yes	No, heterogeneity in study population (due to % genetic disease) I^2 51%	No	Authors declare there Is no conflict of interest.

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

Table of excluded studies

Reference	Reason for exclusion
Parasiliti-Caprino M, Lucatello B, Lopez C, Burrello J, Maletta F, Mistrangelo M, Migliore E, Tassone F, La Grotta A, Pia A, Reimondo G, Giordano R, Giraudo G, Piovesan A, Ciccone G, Deandreis D, Limone P, Orlandi F, Borretta G, Volante M, Mulatero P, Papotti M, Aimaretti G, Terzolo M, Morino M, Pasini B, Veglio F, Ghigo E, Arvat E, Maccario M. Predictors of recurrence of pheochromocytoma and paraganglioma: a multicenter study in Piedmont, Italy. Hypertens Res. 2020 Jun;43(6):500-510. doi: 10.1038/s41440-019-0339-y. Epub 2019 Oct 4. PMID: 31586159.	Wrong design: Prognostic model to predict recurrence without (internal or external) validation
Plouin PF, Amar L, Dekkers OM, Fassnacht M, Gimenez-Roqueplo AP, Lenders JW, Lussey-Lepoutre C, Steichen O; Guideline Working Group. European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. Eur J Endocrinol. 2016 May;174(5):G1-G10. doi: 10.1530/EJE-16-0033. PMID: 27048283.	Wrong design: Guideline
Amar L, Lussey-Lepoutre C, Lenders JW, Djadi-Prat J, Plouin PF, Steichen O. MANAGEMENT OF ENDOCRINE DISEASE: Recurrence or new tumors after complete resection of pheochromocytomas and paragangliomas: a systematic review and meta-analysis. Eur J Endocrinol. 2016 Oct;175(4):R135-45. doi: 10.1530/EJE-16-0189. Epub 2016 Apr 14. PMID: 27080352.	Duplicate article
Barski D. Management and follow up of extra-adrenal phaeochromocytoma. Cent European J Urol. 2014;67(2):156-61. doi: 10.5173/ceju.2014.02.art8. Epub 2014 Jun 23. PMID: 25140230; PMCID: PMC4132600.	Wrong design: Observational single arm; Wrong outcomes
Bhat HS, Tiyadath BN. Management of Adrenal Masses. Indian J Surg Oncol. 2017 Mar;8(1):67-73. doi: 10.1007/s13193-016-0597-y. Epub 2016 Dec 17. PMID: 28127186; PMCID: PMC5236029.	Wrong design: Observational, single arm
Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016 Aug;175(2):G1-G34. doi: 10.1530/EJE-16-0467. PMID: 27390021.	Wrong design: Guideline
Hamidi O, Young WF Jr, Gruber L, Smestad J, Yan Q, Ponce OJ, Prokop L, Murad MH, Bancos I. Outcomes of patients with metastatic phaeochromocytoma and paraganglioma: A systematic review and meta-	Wrong population: Patients with metastasis; Wrong design: Single arm

analysis. Clin Endocrinol (Oxf). 2017 Nov;87(5):440-450. doi: 10.1111/cen.13434. Epub 2017 Aug 17. PMID: 28746746; PMCID: PMC5854189.	
Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF Jr; Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42. doi: 10.1210/jc.2014-1498. Erratum in: J Clin Endocrinol Metab. 2023 Apr 13;108(5):e200. PMID: 24893135.	Wrong study design: Guideline
Lorenz K, Langer P, Niederle B, Alesina P, Holzer K, Nies C, Musholt T, Goretzki PE, Rayes N, Quinkler M, Waldmann J, Simon D, Trupka A, Ladurner R, Hallfeldt K, Zielke A, Saeger D, Pöppel T, Kukuk G, Hötker A, Schabram P, Schopf S, Dotzenrath C, Riss P, Steinmüller T, Kopp I, Vorländer C, Walz MK, Bartsch DK. Surgical therapy of adrenal tumors: guidelines from the German Association of Endocrine Surgeons (CAEK). Langenbecks Arch Surg. 2019 Jun;404(4):385-401. doi: 10.1007/s00423-019-01768-z. Epub 2019 Apr 1. PMID: 30937523.	Wrong study design: Guideline
Suurd DPD, Vorselaars WMCM, Van Beek DJ, Spiering W, Borel Rinkes IHM, Valk GD, Vriens MR. Trends in blood pressure-related outcomes after adrenalectomy in patients with primary aldosteronism: A systematic review. Am J Surg. 2021 Aug;222(2):297-304. doi: 10.1016/j.amjsurg.2020.12.003. Epub 2020 Dec 3. PMID: 33298320.	Wrong outcomes reported
Yip L, Duh QY, Wachtel H, Jimenez C, Sturgeon C, Lee C, Velázquez-Fernández D, Berber E, Hammer GD, Bancos I, Lee JA, Marko J, Morris-Wiseman LF, Hughes MS, Livhits MJ, Han MA, Smith PW, Wilhelm S, Asa SL, Fahey TJ 3rd, McKenzie TJ, Strong VE, Perrier ND. American Association of Endocrine Surgeons Guidelines for Adrenalectomy: Executive Summary. JAMA Surg. 2022 Oct 1;157(10):870-877. doi: 10.1001/jamasurg.2022.3544. PMID: 35976622; PMCID: PMC9386598.	Wrong study design: Executive summary
Benham JL, Eldoma M, Khokhar B, Roberts DJ, Rabi DM, Kline GA. Proportion of Patients With Hypertension Resolution Following Adrenalectomy for Primary Aldosteronism: A Systematic Review and Meta-Analysis. J Clin Hypertens (Greenwich). 2016 Dec;18(12):1205-1212. doi: 10.1111/jch.12916. Epub 2016 Oct 19. PMID: 27759187; PMCID: PMC8031514.	Wrong outcomes reported
Marzano L, Husain-Syed F, Reis T, Ronco C, Zanella M. Assessment of performance of stratum-specific likelihood ratios of the aldosteronoma resolution score for predicting hypertension cure after	No full text available

adrenalectomy for primary aldosteronism: a systematic review and meta-analysis. J Hum Hypertens. 2022 Jul 26. doi: 10.1038/s41371-022-00731-8. Epub ahead of print. PMID: 35882944.	
Meng Z, Dai Z, Huang K, Xu C, Zhang YG, Zheng H, Liu TZ. Long-Term Mortality for Patients of Primary Aldosteronism Compared With Essential Hypertension: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2020 Mar 10;11:121. doi: 10.3389/fendo.2020.00121. PMID: 32210920; PMCID: PMC7075813.	Wrong comparison: Aldosteron-producing adenoma compared to essential hypertension

Literature search strategy

Algemene informatie

Richtlijn: Diagnostiek en chirurgische behandeling Bijniertumoren	
Uitgangsvraag: UV15 Wat is de optimale duur en frequentie van follow-up voor aldosteronproducerend adenoom, cortisolproducerend adenoom of carcinoom, en sporadisch feochromocytoom?	
Database(s): Ovid/Medline, Embase	Datum:6-12-2022
Periode: 2010-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: (Aldosteron- of cortisolproducerend adenoom of carcinoom of feochromocytoom) EN follow-up Vanwege de hoge aantallen wordt gekozen voor de volgende strategie: 1. Starten met systematische reviews en indien gevonden aanvullen met recente studies (RCT OBS) 2. Niets gevonden dan uitvoeren specifiek strategie follow-up (mjr, ti,kw) 3. Niets gevonden dan strategie met recurrence Er zijn (nog) geen sleutelartikelen gevonden	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 6-12-2022 met relevante zoektermen gezocht vanaf 2010 naar systematische reviews over de follow-up van aldosteron- of cortisolproducerende adenomen of carcinomen of feochromocytomen. De literatuurzoekactie leverde 108 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	99	52	108
Totaal	99	52	108

Zoekstrategie

Embase

No.	Query	Results
#18	(#7 OR #8) AND #15	350
#17	#6 AND #15	7
#16	#5 AND #15	38
#15	#14 AND [1-1-2010]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	823
#14	#1 AND #12	2242
#13	#4 AND #12	377
#12	'recurrent disease'/exp OR 'recurren*':ti,ab,kw OR 'relaps*':ti,ab,kw OR recidi*:ti,ab,kw	1363715
#11	#4 AND (#7 OR #8)	1124
#10	#4 AND #6	69
#9	#4 AND #5 SR follow-up	99
#8	'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('major clinical study'/de OR 'clinical study'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	13668006
#7	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	6767914
#6	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	1839814
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	733409
#4	#3 AND [1-1-2010]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	2235
#3	#1 AND #2	1136
#2	'follow up'/exp OR 'follow up':ti,ab,kw OR 'followup':ti,ab,kw	2438782
#1	'primary hyperaldosteronism'/exp OR 'hyperaldosteronism'/exp OR 'pheochromocytoma'/exp OR 'chromaffin cell tumor':ti,ab,kw OR 'chromaffin paraganglioma':ti,ab,kw OR 'phaeochromoblastoma':ti,ab,kw OR 'phaeochromocytoma':ti,ab,kw OR 'pheochromoblastoma':ti,ab,kw OR 'pheochromocytoma':ti,ab,kw OR	49668

	'pheochromocytomata':ti,ab,kw OR 'pheochromocytomatosis':ti,ab,kw OR 'pheochromocytosis':ti,ab,kw OR ((catecholamine NEAR/4 (tumour* OR tumor* OR neoplasm*)):ti,ab,kw) OR ((conn NEAR/3 (syndrome OR disease OR morbus)):ti,ab,kw) OR (((aldosteron* OR cortisol* OR hyperaldosteron*) NEAR/4 (carcinom* OR adenom* OR primary)):ti,ab,kw) OR 'cortisol producing adenoma'/de	

Ovid/Medline

#	Searches	Results
10	5 and 6 SR	52
9	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or ((exp cohort studies/ or epidemiologic studies/ or multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.))	5304815
8	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	4309184
7	exp randomized controlled trial/ or randomized controlled trials as topic/ or random*.ti,ab. or rct?.ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab,kf. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab,kf.	1567553
6	meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.	634320
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1240
4	limit 3 to yr="2010 -Current"	1260
3	1 and 2	2421
2	Follow-Up Studies/ or "follow up".ti,ab,kf. or followup.ti,ab,kf.	1546896
1	exp Hyperaldosteronism/ or Pheochromocytoma/ or chromaffin cell tumor.ti,ab,kf. or chromaffin paraganglioma.ti,ab,kf. or phaeochromoblastoma.ti,ab,kf. or phaeochromocytoma.ti,ab,kf. or pheochromoblastoma.ti,ab,kf. or pheochromocytoma.ti,ab,kf. or pheochromocytomata.ti,ab,kf. or pheochromocytomatosis.ti,ab,kf. or pheochromocytosis.ti,ab,kf. or (catecholamine adj4 (tumour* or tumor* or neoplasm*)).ti,ab,kf. or (conn adj3 (syndrome or disease or morbus)).ti,ab,kf. or ((aldosteron* or cortisol* or hyperaldosteron*) adj4 (carcinom* or adenom* or primary)).ti,ab,kf.	35344

Module 15 – Aandacht bijnierschorsinsufficiëntie

Uitgangsvraag
Bij welke patiëntgroep dient er extra aandacht en behandeling te zijn voor het onstaan van bijnierschorsinsufficiëntie na een unilaterale adrenalectomie?

Inleiding
Bijnierschorsinsufficiëntie kan ontstaan na bijnierchirurgie. Meestal is dit vooraf voorspelbaar. Bijnierschorsinsufficiëntie ontstaat altijd na een bilaterale adrenalectomie of een unilaterale adrenalectomie vanwege het syndroom van Cushing. Bij deze patiënten wordt peri- en postoperatief gestart met een glucocorticoïdstresschema. Dit stressschema wordt afgebouwd en omgezet naar een substitutietherapie met hydrocortison. Bij patiënten na bilaterale adrenalectomie wordt ook fludrocortison gestart, deze substitutietherapie is levenslang. Bij patiënten met het syndroom van Cushing na resectie van een unilateraal cortisol producerend bijnieradenoom wordt de hydrocortison geleidelijk verder afgebouwd en gestopt als de hypothalamus-hypofyse-bijnier as volledig is hersteld. Soms is volledig afbouwen niet mogelijk en blijven sommige patiënten levenslang afhankelijk van hydrocortison.

Ook bij patiënten na een unilaterale adrenalectomie kan bijnierschorsinsufficiëntie ontstaan, onverwacht, postoperatief op de verpleegafdeling of na ontslag. Als deze conditie niet tijdig wordt onderkend, dan kan dit tot een levensbedreigende bijniercrisis (vroeger ook wel Addison crisis genoemd) leiden. Factoren die hieraan bijdragen zijn onvoldoende preoperatieve informatie over bestraling van de contralaterale bijnier, (gedeeltelijke) resectie van de contralaterale bijnier of een onvoldoende functionerende contralaterale bijnier om andere redenen. Daarnaast kan een niet-herkend subklinisch syndroom van Cushing (co-productie van cortisol), met name bij primair hyperaldosteronisme, bijdragen aan de ontwikkeling van postoperatieve bijnierschorsinsufficiëntie.

Bij patiënten met subklinisch syndroom van Cushing ontwikkelt ongeveer de helft van de patiënten een bijnierschorsinsufficiëntie na een adrenalectomie (Di Dalmazi, 2014). Om een onbehandelde bijnierschorsinsufficiëntie en/of een bijniercrisis te voorkomen is het wenselijk om vooraf in te kunnen schatten welke patiënten at risk zijn om bijnierschorsinsufficiëntie te ontwikkelen na unilaterale adrenalectomie.

Search and select
A search was initiated to find a review, preferably a systematic review, measuring the effect of using a prediction model to predict whether a patient is at high risk for developing adrenal insufficiency after unilateral adrenalectomy. Such research is very rare.

A systematic and pragmatic review of the literature was performed to answer the following question: Is there a model available that can predict the development of adrenocortical insufficiency after unilateral adrenalectomy?

P (Patients)	Patients after unilateral adrenalectomy for an adrenal tumor, without confirmed diagnosis of Cushing's syndrome
I (Intervention)	(validated) prediction model that can predict the development of adrenocortical insufficiency after adrenalectomy
C (Control)	care as usual (no model)
O (Outcomes)	predictive value of the model (area under the curve)
T/S (Timing and Setting)	after adrenalectomy, before going to the nursing ward or home

Relevant outcome measures
The guideline development group considered area under the curve (AUC) as a critical outcome measure for decision making. The working group defined the performance of the included models as follows:

- 0.7≤AUC<0.8: acceptable
- 0.8≤AUC<0.9: excellent
- AUC≥0.9: outstanding

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 03-02-2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 92 hits. Studies were selected based on the following criteria:

- The study population had to meet the criteria as defined in the PICO;
- The intervention and comparison had to be as defined in the PICO;
- Outcomes had to be as defined in the PICO;
- Articles written in English or Dutch

Based on title and abstract screening 21 studies were selected. After reading the full text, all 21 studies were excluded (see the table with reasons for exclusion under the tab Methods), and therefore no studies could be included.

Results
No studies were included in the analysis of the literature because the lack of comparison between a (validated) prediction model compared to no model or usual care . However, there are seven individual studies (and one systematic review who included two of these individual studies) that describe risk factors regarding the development of adrenocortical insufficiency after an adrenalectomy. No GRADE assessment will be applied to these studies, but they will be described briefly below.

Summary of literature
Description of studies
Wang (2021) performed a retrospective study with 66 patients that had a confirmed diagnosis of APA based on aldosterone-to-renin ratio (ARR), saline infusion testing (SIT) and underwent non-ACTH stimulated adrenal vein sampling (AVS) for subtyping. The aim of the study was to identify variables measured pre-operatively that are associated with post-operative adrenal insufficiency, to facilitate early detection and treatment of this condition. In order to investigate associations between preoperative variables and the occurrence of postoperative adrenal insufficiency, linear regression models were built. Nine variables fell into this category. Of those, two could not be used because more than 20% of the data were missing. From the remaining seven variables, they excluded another three because they had no significant contribution to the model. The remaining four variables were insulin during OGTT at 60 min, salivary cortisol at 20:00, baseline cortisone and baseline estradiol during ACTH test. According to standard coefficients, the strength of the effects was highest for insulin during OGTT at 60 min, followed by salivary cortisol at 20:00, baseline cortisone and baseline estradiol. They concluded that their results suggests that glucocorticoid co-secretion is correlated with the development of post-operative adrenal insufficiency. Addition of steroid profiles improved the accuracy of prediction, but cross validation revealed lack of reliability in the prediction of adrenal insufficiency.

Di Dalmazi (2014) performed a systematic review to summarize the prevalence of postoperative adrenal insufficiency in patients with subclinical hypercortisolism compared with Cushing syndrome. The second aim was to analyze the potential predictive factors for development of postoperative adrenal insufficiency. In total, Di Dalmazi (2014) included 28 studies. Regarding the scope of this literature review, only the two studies who reported potential predictive factors for development of postoperative adrenal insufficiency, are described (Ellen-Vainicher, 2010).

Eller-Vainicher (2010) performed a prospective cohort study of 60 patients who underwent surgical removal of the adrenal incidentaloma. The aim of this study was to evaluate whether parameters of HPA axis function could predict post-surgical hypocortisolism. Twenty-one patients with baseline cortisol > 5 µg/dl and stimulated cortisol levels > 22 µg/dl were considered not affected with adrenal insufficiency (group A) and 34 patients with baseline cortisol < 5 µg/dl and/or stimulated cortisol levels < 16 µg/dl were considered hypoadrenal (group B), were compared. The presence of at least two alterations among 1 mg-DST > 5.0 µg/dL, elevated Urinary Free Cortisol (UFC), elevated Midnight Serum Cortisol (MSC) and ACTH < 10 pg/ml was associated with the highest odds ratio for predicting post-surgical hypocortisolism. This association was independent of age, BMI, size of the adenoma and duration of pre-surgical follow-up.
Eller-Vainicher (2010) concluded that no parameters or combination of parameters have enough diagnostic accuracy to predict the possibility of post-surgical hypocortisolism.

Eller-Vainicher (2020) performed a retrospective study of 60 patients who underwent surgical removal of the adrenal mass due to presence of hypercortisolism and/or on the basis of the size of the lesion. The aim of the study was to define the absence of hypercortisolism in patients with adrenal incidentaloma by assessing the cut-offs of the 1 milligram overnight dexamethasone suppression test and other parameters of HPA axis activity. Patients with (n=39) and without (n=21) post-surgical hypocortisolism (PSH) were compared.
The authors considered the F-1mgDST test the only test with enough reliability to be investigated as a possible marker for absence of PSH in this cohort. By using a F-1mgDST cut-off set at 1.2 µg/dL, 100% sensitivity and positive predictive value, 42.9% specificity and 76.5% negative predictive value, were obtained.

Results
Predictive value of the model (area under the curve) (critical)
Not applicable.

Level of evidence of the literature
Predictive value of the model (area under the curve) (critical)
Not applicable.

Conclusions
Predictive value of the model (area under the curve) (critical)

No GRADE	No evidence was found regarding the effect of any prediction model that predicts the development of adrenal insufficiency after adrenalectomy on the outcome predictive value of the model when compared with usual care in patients after adrenalectomy. *Source: -*

Overwegingen – van bewijs naar aanbeveling

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

Het is niet duidelijk wat risicofactoren zijn voor het ontstaan van bijnierinsufficiëntie na een unilaterale adrenalectomie bij patiënten met een bijniertumor zonder bewezen syndroom van Cushing. Literatuuronderzoek leverde geen studies op welke een gevalideerd predictiemodel hebben vergeleken met usual care of geen model. Hier ligt dus een kennislacune en meer onderzoek over deze risicofactoren is gewenst.

Er zijn wel een aantal studies gevonden die risicofactoren op het ontstaan van bijnierinsufficiëntie hebben gerapporteerd. Omdat dit geen studies zijn die de vergelijking hebben gemaakt, zijn deze studies niet gegradeerd volgens de GRADE methodiek maar wel beschreven in de literatuursamenvatting. Zeven studies hebben de risicofactoren beschreven (Wang, 2021; Suguira, 2018; Ellen-Vainicher, 2010; Ellen-Vainicher, 2020). Gevonden associaties tussen de risicofactoren en het ontstaan van post-operatieve bijnierinsufficiëntie worden per studie in onderstaande tabel 1 weergegeven.

Tabel 1. Risicofactoren op onstaan van post-operatieve bijnierinsufficiëntie

Studie	Risicofactoren
Wang (2021)	Glucocorticoid co-secretion (low insulin during pre-operative OGTT and insufficient suppression of glucocorticoids following dexamethasone)
Ellen-Vainicher (2010)	Elevated UFC /MSC levels
Ellen-Vainicher (2020)	the F-1mgDST test cut-off set at 1.2 µg/dL

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

Het is belangrijk om bijnierschorsinsufficiëntie tijdig te herkennen en te behandelen, met als doel zowel postoperatieve bijniercrises als onopgemerkte periodes van bijnierschorsinsufficiëntie te voorkomen. Na de diagnose is het essentieel dat patiënten en hun naasten voorlichting ontvangen over het verhogen van glucocorticoïden in stresssituaties, evenals training in het toedienen van een noodinjectie met hydrocortison om een (dreigende) bijniercrisis te voorkomen.
Het is aan te bevelen dat een verpleegkundig specialist (of gespecialiseerde verpleegkundige), werkzaam binnen de endocrinologie, direct betrokken wordt bij de behandeling en begeleiding. Deze professional richt zich op het ontwikkelen van zelfmanagementvaardigheden en heeft speciale aandacht voor de psychosociale impact van de aandoening. Daarnaast wordt geadviseerd patiënten door te verwijzen naar de patiëntvereniging, zoals de Bijniervereniging NVACP of Nederlandse Hypofyse Stichting.

Kosten (middelenbeslag)

Er zijn geen data over de kosten, maar elke preoperatieve diagnostische test die een risico op een latere postoperatieve bijnierschorsinsufficiëntie zou kunnen voorspellen zou mogelijk langere opnames, heropname en andere kosten van deze potentieel gevaarlijke complicatie kunnen voorkomen. Complicaties zijn over het algemeen kostbaar en dus als deze voorkomen kunnen worden bespaard dit vaak veel middelen.

De andere kant is dat de kans op bijnierschorsinsufficiëntie na unilaterale adrenalectomie bij patiënten *zonder* (subklinisch) syndroom van Cushing en aanwezigheid van risicofactoren, zeer klein is.

Derhalve kunnen deze patiënten de volgende dag zonder diagnostische testen en bij algemeen welbevinden ontslagen worden. Behandel en verricht alleen aanvullend

onderzoek naar bijnierschorsinsufficiëntie indien postoperatief klinische verdenking is op bijnierschorsinsufficiëntie.

Aanvaardbaarheid, haalbaarheid en implementatie

Het huidig gehanteerde stressschema voor patiënten die een bilaterale adrenalectomie moeten ondergaan of geopereerd worden vanwege de ziekte van Cushing is vastgelegd in onder andere de kwaliteitsstandaard bijnieraandoeningen (BijnierNET, 2017). Ziekenhuisprotocollen op afdelingen zijn hierop ingesteld en patiënten worden erop voorbereid. Er zijn geen betrouwbare parameters om te voorspellen of een patiënt die unilaterale adrenalectomie moet ondergaan ook postoperatief bijnierschorsinsufficiëntie ontwikkelt. Daarom is er geen aanleiding gevonden om de huidige klinische praktijk aan te passen.

Aanbeveling

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

Er zijn geen studies waarin parameters gevonden zijn die het ontstaan van postoperatieve bijnierschorsinsufficiëntie voldoende betrouwbaar voorspellen. Na een adrenalectomie beiderzijds of een unilaterale adrenalectomie vanwege het syndroom van Cushing wordt bijnierschorsinsufficiëntie behandeld door een peri- en postoperatief glucocorticoïdstressschema (BijnierNET, 2017). Dit schema wordt postoperatief afgebouwd of omgezet naar substitutie therapie met hydrocortison.

Risicofactoren voor het ontstaan van bijnierschorsinsufficiëntie na een unilaterale adrenalectomie zijn:

- bestraling van de contralaterale bijnier,
- (gedeeltelijke) resectie van de contralaterale bijnier
- Een onvoldoende functionerende contralaterale bijnier.
- Een niet-herkend subklinisch syndroom van Cushing
- Co-secretie van cortisol door aldosteron producerende adenomen

Deze factoren moeten voor operatie in ogenschouw worden genomen bij de risico inschatting op postoperatieve bijnierinsufficiëntie. Een subklinisch syndroom van Cushing dient bij een bijnierincidentaloom altijd biochemisch uitgesloten te worden. Evaluatie van eventuele co-secretie van cortisol door aldosteron-producerende adenomen kan overwogen worden. Omdat een bijniercrisis potentieel gevaarlijk is, dienen patiënten postoperatief geobserveerd te worden op verschijnselen die kunnen passen bij bijnierschorsinsufficiëntie. Patiënten en hun omgeving dienen bij ontslag geïnstrueerd te worden (door de zaalarts of verpleegkundige van de afdeling) over klachten die kunnen passen bij bijnierschorsinsufficiëntie of dreigende bijniercrisis zodat zij deze kunnen herkennen en tijdig contact kunnen opnemen.

Alle patiënten met bijnierschorsinsufficiëntie moeten zelfmanagementvaardigheden ontwikkelen om adequaat te handelen in stresssituaties of bij een (dreigende) bijniercrisis. Het is daarom van belang dat zij en diens naasten voorlichting ontvangen over het toepassen van (orale) dosis verhoging en training in het toedienen van een noodinjectie met hydrocortison ter preventie van een (dreigende) bijniercrisis. De inhoud van deze voorlichting en de uniforme stressinstructies is uitgewerkt in de kwaliteitstandaard bijnieraandoeningen (BijnierNET, 2017).

De kans op bijnierschorsinsufficiëntie na unilaterale adrenalectomie bij patiënten zonder (subklinisch) syndroom van Cushing en aanwezigheid van risicofactoren is zeer klein.

Inventariseer voorafgaand aan een unilaterale adrenalectomie risicofactoren voor het ontstaan van bijnierschorsinsufficiëntie. Risicofactoren voor het ontstaan van postoperatieve bijnierschorsinsufficiëntie zijn:

- Bestraling van de contralaterale bijnier;
- (Gedeeltelijke) resectie van de contralaterale bijnier;
- Een onvoldoende functionerende contralaterale bijnier;
- Een niet-herkend subklinisch syndroom van Cushing;
- Co-secretie van cortisol door aldosteron producerende adenomen.

Behandel patiënten met bilaterale adrenalectomie, (subklinisch) syndroom van Cushing en/of patiënten met de aanwezigheid van risicofactoren op bijnierschorsinsufficiëntie peri- en postoperatief met een glucocorticoïd stressschema.

Bouw de hydrocortison af naar substitutie therapie. Overweeg (behalve bij bilaterale adrenalectomie) om op dag 4-6 het plasma cortisol na 24 uur geen inname van hydrocortison te bepalen. Beoordeel op basis van de uitslag of substitutie therapie en/of stressinstructies geïndiceerd is. Start bij bilaterale adrenalectomie fludrocortison als de dag dosering hydrocortison minder is dan 50 mg (Pazderska, 2017; Arlt, 2009). Bouw de hydrocortison bij patiënten met syndroom van Cushing poliklinisch geleidelijk af en evaluaeer de hypofyse-bijnier-as.

Geef patiënten met bijnierschorsinsufficiëntie en diens naasten voorlichting over het toepassen van (orale) dosis verhoging en training in het toedienen van een noodinjectie met hydrocortison ter preventie van een (dreigende) bijniercrisis. De inhoud van deze voorlichting en de uniforme stressinstructies zijn uitgewerkt in de kwaliteitsstandaard bijnieraandoeningen.

De kans op bijnierschorsinsufficiëntie na unilaterale adrenalectomie bij patiënten zonder (subklinisch) syndroom van Cushing en aanwezigheid van risicofactoren is zeer klein. Behandel en verricht aanvullend onderzoek naar bijnierschorsinsufficiëntie alleen indien postoperatief klinische verdenking is op bijnierschorsinsufficiëntie. Instrueer de patiënt en diens omgeving over de zeer kleine kans op het ontstaan van bijnierschorsinsufficiëntie. Adviseer om contact op te nemen bij:

- Ernstige vermoeidheid en/of zwakte
- Duizeligheid
- Misselijkheid
- Braken
- Slaperigheid, sufheid

Zie ook het stroomschema.

Literatuur

Arlt W. The approach to the adult with newly diagnosed adrenal insufficiency. J Clin Endocrinol Metab. 2009 Apr;94(4):1059-67. doi: 10.1210/jc.2009-0032. PMID: 19349469.

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Di Dalmazi G, Berr CM, Fassnacht M, Beuschlein F, Reincke M. Adrenal function after adrenalectomy for subclinical hypercortisolism and Cushing's syndrome: a systematic review of the literature. J Clin Endocrinol Metab. 2014 Aug;99(8):2637-45. doi: 10.1210/jc.2014-1401. Epub 2014 May 30. PMID: 24878052.

Eller-Vainicher C, Morelli V, Salcuni AS, Torlontano M, Coletti F, Iorio L, Cuttitta A, Ambrosio A, Vicentini L, Carnevale V, Beck-Peccoz P, Arosio M, Ambrosi B, Scillitani A, Chiodini I. Post-surgical hypocortisolism after removal of an adrenal incidentaloma: is it predictable by an accurate endocrinological work-up before surgery? Eur J Endocrinol. 2010 Jan;162(1):91-9. doi: 10.1530/EJE-09-0775. Epub 2009 Oct 1. PMID: 19797503.

Eller-Vainicher C, Morelli V, Aresta C, Salcuni AS, Falchetti A, Carnevale V, Persani L, Scillitani A, Chiodini I. Defining Nonfunctioning Adrenal Adenomas on the Basis of the Occurrence of Hypocortisolism after Adrenalectomy. J Endocr Soc. 2020 Jun 19;4(8):bvaa079. doi: 10.1210/jendso/bvaa079. PMID: 32699828; PMCID: PMC7365697.

Kahramangil B, Montorfano L, Gutierrez D, Erten O, Zhou K, Li D, Rao P, Berber E. Biochemical assessment of adrenal insufficiency after adrenalectomy for non-cortisol secreting tumors: clinical correlation and recommendations. Surg Endosc. 2022 Oct;36(10):7638-7646. doi: 10.1007/s00464-022-09232-8. Epub 2022 Apr 12. PMID: 35414133.

Lin D, Lin J, Hu X, Liu Y, Zhang J, Zhang L, Jiang J, Li X, Guo J. Preoperative prognostic nomogram for prophylactic steroid treatment of patients with subclinical Cushing's syndrome. Transl Androl Urol. 2021 Jan;10(1):426-437. doi: 10.21037/tau-20-1108. PMID: 33532330; PMCID: PMC7844482.

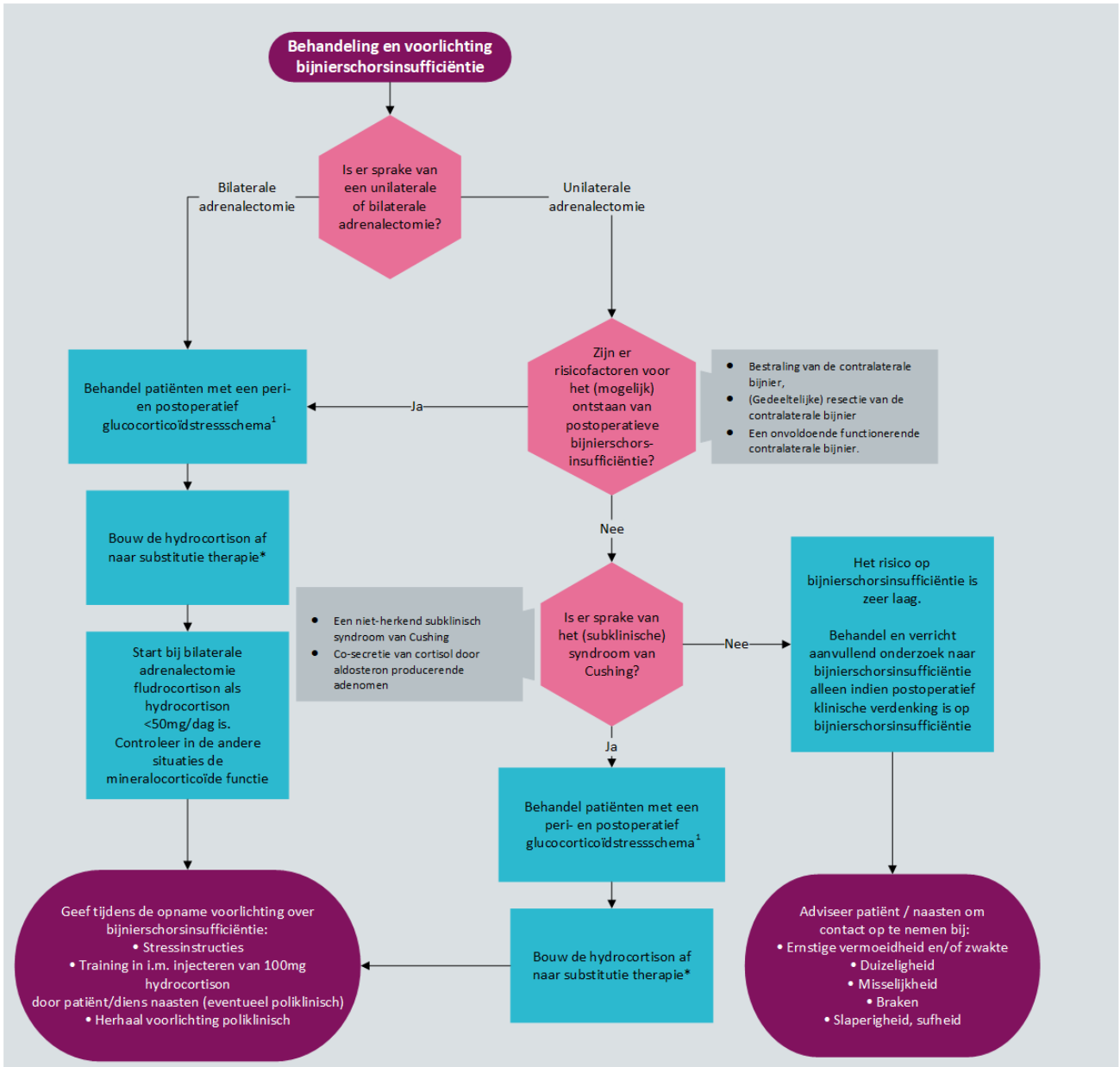
Pazderska A, Pearce SH. Adrenal insufficiency - recognition and management. Clin Med (Lond). 2017 Jun;17(3):258-262. doi: 10.7861/clinmedicine.17-3-258. PMID: 28572228; PMCID: PMC6297573.

Sugiura M, Imamura Y, Kawamura K, Yamamoto S, Sazuka T, Nakamura K, Sakamoto S, Nagano H, Koide H, Tanaka T, Imamoto T, Komiya A, Ichikawa T. Contralateral adrenal width predicts the duration of prolonged post-surgical steroid replacement for subclinical Cushing syndrome. Int J Urol. 2018 Jun;25(6):583-588. doi: 10.1111/iju.13566. Epub 2018 Apr 12. PMID: 29651813.

Wang X, Heinrich DA, Kunz SL, Heger N, Sturm L, Uhl O, Beuschlein F, Reincke M, Bidlingmaier M. Characteristics of preoperative steroid profiles and glucose metabolism in patients with primary aldosteronism developing adrenal insufficiency after adrenalectomy. Sci Rep. 2021 May 27;11(1):11181. doi: 10.1038/s41598-021-90901-4. PMID: 34045650; PMCID: PMC8160266.

Bijlagen bij module Aandacht bijnierinsufficiëntie

Stroomschema Bijnierinsufficiëntie



Evidence tables
Niet van toepassing

Table of excluded studies

Reference	Reason for exclusion
Zelinka T, Petrák O, Waldauf P, Zítek M, Holaj R, Forejtová L, Michalský D, Novák K, Dušková J, Springer D, Widimský J Jr. Postoperative adrenal insufficiency in Conn's syndrome-does it occur frequently? J Hum Hypertens. 2022 Jun;36(6):510-516. doi: 10.1038/s41371-021-00618-0. Epub 2021 Oct 6. PMID: 34615973.	Not a systematic review; Only individual parameters after surgery are reported.
Kahramangil B, Montorfano L, Gutierrez D, Erten O, Zhou K, Li D, Rao P, Berber E. Biochemical assessment of adrenal insufficiency after adrenalectomy for non-cortisol secreting tumors: clinical correlation and recommendations. Surg Endosc. 2022 Oct;36(10):7638-7646. doi: 10.1007/s00464-022-09232-8. Epub 2022 Apr 12. PMID: 35414133.	No prediction model; only univariate analyses.
Wang X, Heinrich DA, Kunz SL, Heger N, Sturm L, Uhl O, Beuschlein F, Reincke M, Bidlingmaier M. Characteristics of preoperative steroid profiles and glucose metabolism in patients with primary aldosteronism developing adrenal insufficiency after adrenalectomy. Sci Rep. 2021 May 27;11(1):11181. doi: 10.1038/s41598-021-90901-4. PMID: 34045650; PMCID: PMC8160266.	No prediction model; only univariate analyses
Wang D, Li HZ, Zhang YS, Wang L, Ji ZG. Is Prophylactic Steroid Treatment Mandatory for Subclinical Cushing Syndrome After Unilateral Laparoscopic Adrenalectomy? Surg Laparosc Endosc Percutan Tech. 2019 Feb;29(1):31-35. doi: 10.1097/SLE.0000000000000585. PMID: 30300254.	No multivariate model; Comparison between patients with and without adrenal insufficiency for baseline characteristics
Sugiura M, Imamura Y, Kawamura K, Yamamoto S, Sazuka T, Nakamura K, Sakamoto S, Nagano H, Koide H, Tanaka T, Imamoto T, Komiya A, Ichikawa T. Contralateral adrenal width predicts the duration of prolonged post-surgical steroid replacement for subclinical Cushing syndrome. Int J Urol. 2018 Jun;25(6):583-588. doi: 10.1111/iju.13566. Epub 2018 Apr 12. PMID: 29651813.	No comparison of prediction model versus no prediction model/care as usual
Di Dalmazi G, Berr CM, Fassnacht M, Beuschlein F, Reincke M. Adrenal function after adrenalectomy for subclinical hypercortisolism and Cushing's syndrome: a systematic review of the literature. J Clin Endocrinol Metab. 2014 Aug;99(8):2637-45. doi: 10.1210/jc.2014-1401. Epub 2014 May 30. PMID: 24878052.	No comparison of prediction model versus no prediction model/care as usual

Honda K, Sone M, Tamura N, Sonoyama T, Taura D, Kojima K, Fukuda Y, Tanaka S, Yasuno S, Fujii T, Kinoshita H, Ariyasu H, Kanamoto N, Miura M, Yasoda A, Arai H, Ueshima K, Nakao K. Adrenal reserve function after unilateral adrenalectomy in patients with primary aldosteronism. J Hypertens. 2013 Oct;31(10):2010-7. doi: 10.1097/HJH.0b013e3283635789. PMID: 23846863.	Wrong population; no adrenal insufficiency as outcome; only univariate analyses
Eller-Vainicher C, Morelli V, Salcuni AS, Torlontano M, Coletti F, Iorio L, Cuttitta A, Ambrosio A, Vicentini L, Carnevale V, Beck-Peccoz P, Arosio M, Ambrosi B, Scillitani A, Chiodini I. Post-surgical hypocortisolism after removal of an adrenal incidentaloma: is it predictable by an accurate endocrinological work-up before surgery? Eur J Endocrinol. 2010 Jan;162(1):91-9. doi: 10.1530/EJE-09-0775. Epub 2009 Oct 1. PMID: 19797503.	No comparison of prediction model versus no prediction model/care as usual
Heinrich DA, Adolf C, Holler F, Lechner B, Schneider H, Riester A, Nirschl N, Sturm L, Wang X, Ladurner R, Seidensticker M, Bidlingmaier M, Beuschlein F, Reincke M. Adrenal Insufficiency After Unilateral Adrenalectomy in Primary Aldosteronism: Long-Term Outcome and Clinical Impact. J Clin Endocrinol Metab. 2019 Nov 1;104(11):5658-5664. doi: 10.1210/jc.2019-00996. PMID: 31225874.	Wrong outcome; no comparison of prediction model versus no prediction model/care as usual
Morelli V, Minelli L, Eller-Vainicher C, Palmieri S, Cairoli E, Spada A, Arosio M, Chiodini I. Predictability of hypoadrenalism occurrence and duration after adrenalectomy for ACTH-independent hypercortisolism. J Endocrinol Invest. 2018 Apr;41(4):485-493. doi: 10.1007/s40618-017-0788-6. Epub 2017 Nov 18. PMID: 29151238.	Wrong population
Hurtado MD, Cortes T, Natt N, Young WF Jr, Bancos I. Extensive clinical experience: Hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess. Clin Endocrinol (Oxf). 2018 Dec;89(6):721-733. doi: 10.1111/cen.13803. Epub 2018 Jul 23. PMID: 29968420; PMCID: PMC6246804.	Wrong population
Prete A, Paragliola RM, Bottiglieri F, Rota CA, Pontecorvi A, Salvatori R, Corsello SM. Factors predicting the duration of adrenal insufficiency in patients successfully treated for Cushing disease and nonmalignant primary adrenal Cushing syndrome. Endocrine. 2017 Mar;55(3):969-980. doi: 10.1007/s12020-016-1007-5. Epub 2016 Jul 9. PMID: 27395418.	Wrong population; wrong outcome
Quinkler M, Kienitz T. The ISAQ Score Does Not Predict Adrenal Crisis in Patients with Primary Adrenal	Wrong outcome; wrong population

Insufficiency. Exp Clin Endocrinol Diabetes. 2022 Aug;130(8):554-560. doi: 10.1055/a-1734-2466. Epub 2022 Mar 3. PMID: 35240692.	
Lin D, Lin J, Hu X, Liu Y, Zhang J, Zhang L, Jiang J, Li X, Guo J. Preoperative prognostic nomogram for prophylactic steroid treatment of patients with subclinical Cushing's syndrome. Transl Androl Urol. 2021 Jan;10(1):426-437. doi: 10.21037/tau-20-1108. PMID: 33532330; PMCID: PMC7844482.	No comparison of prediction model versus no prediction model/care as usual
Eller-Vainicher C, Morelli V, Aresta C, Salcuni AS, Falchetti A, Carnevale V, Persani L, Scillitani A, Chiodini I. Defining Nonfunctioning Adrenal Adenomas on the Basis of the Occurrence of Hypocortisolism after Adrenalectomy. J Endocr Soc. 2020 Jun 19;4(8):bvaa079. doi: 10.1210/jendso/bvaa079. PMID: 32699828; PMCID: PMC7365697.	No comparison of prediction model versus no prediction model/care as usual
Sarkis P, Rabilloud M, Lifante JC, Siamand A, Jouanneau E, Gay E, Chaffanjon P, Chabre O, Raverot G. Bilateral adrenalectomy in Cushing's disease: Altered long-term quality of life compared to other treatment options. Ann Endocrinol (Paris). 2019 Feb;80(1):32-37. doi: 10.1016/j.ando.2018.01.002. Epub 2018 Sep 19. PMID: 30243473.	Wrong population; no multivariable analysis
Chen Y, Scholten A, Chomsky-Higgins K, Nwaogu I, Gosnell JE, Seib C, Shen WT, Suh I, Duh QY. Risk Factors Associated With Perioperative Complications and Prolonged Length of Stay After Laparoscopic Adrenalectomy. JAMA Surg. 2018 Nov 1;153(11):1036-1041. doi: 10.1001/jamasurg.2018.2648. PMID: 30090934; PMCID: PMC6584328.	Wrong outcome
Starker LF, Christakis I, Julien JS, Schwarz K, Graham P, Grubbs EG, Lee JE, Perrier ND. Considering Postoperative Functional Hypoaldosteronism after Unilateral Adrenalectomy. Am Surg. 2017 Jun 1;83(6):598-604. PMID: 28637561.	Wrong outcome
Ricciato MP, Di Donna V, Perotti G, Pontecorvi A, Bellantone R, Corsello SM. The role of adrenal scintigraphy in the diagnosis of subclinical Cushing's syndrome and the prediction of post-surgical hypoadrenalism. World J Surg. 2014 Jun;38(6):1328-35. doi: 10.1007/s00268-014-2482-6. PMID: 24615601.	Wrong outcome; no multivariable analysis
Yap SA, Alibhai SM, Abouassaly R, Timilshina N, Finelli A. Do we continue to unnecessarily perform ipsilateral adrenalectomy at the time of radical nephrectomy? A population based study. J Urol. 2012 Feb;187(2):398-404. doi: 10.1016/j.juro.2011.10.030. Epub 2011 Dec 15. PMID: 22177155.	Wrong population

Brauckhoff M, Dralle H. Funktionserhaltende Adrenalektomie bei Nebennierentumoren [Function-preserving adrenalectomy for adrenal tumors]. Chirurg. 2012 Jun;83(6):519-27. German. doi: 10.1007/s00104-011-2192-7. PMID: 22580725.	Wrong population

Literature search strategy

Algemene informatie

Richtlijn: NVVH - Bijniertumoren	
Uitgangsvraag: Bij welke patiëntgroepen moet extra aandacht zijn voor het onstaan van bijnierinsufficientie na een bijnieroperatie/na een unilaterale adrenalectomie?	
Database(s): Ovid/Medline, Embase	Datum:3-2-2023
Periode: 2010-	Talen: nvt
Literatuurspecialist: Ingeborg van Dusseldorp	
BMI zoekblokken: voor verschillende opdrachten wordt (deels) gebruik gemaakt van de zoekblokken van BMI-Online https://blocks.bmi-online.nl/ Bij gebruikmaking van een volledig zoekblok zal naar de betreffende link op de website worden verwezen.	
Toelichting: Voor deze vraag is gezocht met de volgende concepten: Adrenalectomie EN bijnierschorsinsufficiëntie EN prognostisch model Het sleutelartikel wordt gevonden	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 3-2-2023 met relevante zoektermen gezocht vanaf 2010 naar prognostische studies over het ontstaan van bijnierschorsinsufficiëntie na adrenalectomie. De literatuurzoekactie leverde 92 unieke treffers op.	

Zoekopbrengst

	EMBASE	**OVID/MEDLINE**	**Ontdubbeld**
SRs	90	21	92
RCTs			
Observationele studies			
Prognostisch			
Totaal			

Zoekstrategie

Embase

No.	Query	Results
#8	#1 AND #7 sleutelartikel gevonden	1
#7	#5 AND #6	90
#6	'adrenal cortex insufficiency'/exp OR ((adren* NEAR/3 (insufficien* OR fail* OR hypofunction OR dysfunction)):ti,ab,kw)	36347
#5	#4 AND [1-1-2010]/sd NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	856
#4	#2 AND #3	1714
#3	'area under the curve'/exp OR 'brier score'/exp OR 'computer prediction'/exp OR 'c statistic'/exp OR 'c statistics'/exp OR 'integrated discrimination improvement'/exp OR 'net reclassification improvement'/exp OR 'net reclassification index'/exp OR 'prediction'/exp OR 'predictive model'/exp OR 'predictive modeling'/exp OR 'predictive validity'/exp OR 'predictive value'/exp OR 'regression analysis'/exp OR 'statistical model'/exp OR 'area under the curve':ti,ab,kw OR 'brier score*':ti,ab,kw OR 'c statistic*' OR 'computer prediction':ti,ab,kw OR 'decision curve anal*':ti,ab,kw OR (('net reclassification' NEAR/2 (improvement OR index)):ti,ab,kw) OR (((predict* OR statistical*) NEAR/3 (model* OR validity OR value)):ti,ab,kw) OR 'proportional hazards model*':ti,ab,kw OR 'r square*':ti,ab,kw OR regression:ti,ab,kw OR predict*:ti OR multivariate:ti,ab,kw OR multivariab*:ti,ab,kw OR 'biochemical test'/exp OR 'biochemical test*':ti,ab,kw OR (((serum OR operat* OR surg*) NEAR/3 cortisol):ti,ab,kw) OR (((adrenocortical OR adrenalcortical OR 'adrenal cortical') NEAR/3 function*):ti,ab,kw)	3138264
#2	'adrenalectomy'/exp OR adrenalectom*:ti,ab,kw OR ((adrenal* NEAR/3 (surger* OR resecti* OR extirpat* OR remov*)):ti,ab,kw)	36351
#1	'biochemical assessment of adrenal insufficiency after adrenalectomy for non-cortisol secreting tumors: clinical correlation and recommendations' sleutelartikel	1

Ovid/Medline

#	Searches	Results
7	5 and 6	21
6	Area Under Curve/ or exp Forecasting/ or "Predictive Value of Tests"/ or exp Multivariate Analysis/ or exp Regression Analysis/ or exp Models, Statistical/ or area under the curve.ti,ab,kf. or brier score*.ti,ab,kf. or c statistic*.ti,ab,kf. or computer prediction.ti,ab,kf. or decision curve anal*.ti,ab,kf. or (net reclassification adj2 (improvement or index)).ti,ab,kf. or ((predict* or statistical*) adj3 (model* or validity or value)).ti,ab,kf. or proportional hazards model*.ti,ab,kf. or r square*.ti,ab,kf. or regression.ti,ab,kf. or predict*.ti. or multivaria*.ti,ab,kf.	2360510
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	220
4	limit 3 to yr="2010 -Current"	250
3	1 and 2	901
2	exp Adrenal Insufficiency/ or (adren* adj3 (insufficien* or fail* or hypofunction or dysfunction)).ti,ab,kf.	19738
1	Adrenalectomy/ or adrenalectom*.ti,ab,kf. or (adrenal* adj3 (surger* or resecti* or extirpat* or remov*)).ti,ab,kf.	28573

Bijlage 1 – Kennislacunes

Inleiding
Tijdens de ontwikkeling van de richtlijn/module 'Diagnostiek en behandeling van bijniertumoren' is systematisch gezocht naar onderzoeksbevindingen die nuttig konden zijn voor het beantwoorden van de uitgangsvragen. Een deel (of een onderdeel) van de hiervoor opgestelde zoekvragen is met het resultaat van deze zoekacties te beantwoorden, een groot deel echter niet. Door gebruik te maken van de evidence-based methodiek (EBRO) is duidelijk geworden dat er nog kennislacunes bestaan. De werkgroep is van mening dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk. Om deze reden heeft de werkgroep per module aangegeven op welke vlakken nader onderzoek gewenst is.

Module Diagnostiek bijnier incidentaloom

- Verdere grote cohortstudies waarin selectiebias zou moeten worden geminimaliseerd en wordt uitgegaan van de juiste patiëntengroep kunnen helpen de additionele waarde van washout als parameter aan te tonen.
- In de bestudeerde literatuur wordt een lagere incidentie van maligniteit in oudere patiënten met incidentalomen genoemd. Verdere studies moeten uitwijzen of een afkappunt in leeftijd kan worden gehanteerd om een ander risicostratificatiemodel toe te passen.
- In de huidige uitgangsvraag is gekozen voor het onderzoeken van de waarde van CT in het differentiëren van incidentalomen. Technieken als MRI en FDG-PET worden echter erkend als mogelijke modaliteiten om incidentalomen te evalueren. Verder onderzoek zou moeten leiden tot scherpere aanbevelingen wanneer deze technieken in de diagnostische work-up in te zetten.

Module Diagnostiek morbus Conn
Adrenal Vein Sampling (AVS) is beperkt beschikbaar in Nederland maar wel de richtlijn en aan te bevelen. Natuurlijk is het reden voor verder onderzoek naar een beter beschikbare niet-invasieve diagnostiek (zoals Pentixafor PET-CT).

P: Patiënten met primair hyperaldosteronisme (m. Conn)
I: Niet-invasieve diagnostiek (Pentixafor PET-CT)
C: Adrenal Vein Sampling (AVS)
O: Bloeddrukcontrole, normokalemie, complicaties, kosten en kwaliteit van leven

Module Behandeling morbus Conn
Toekomstige studies zullen renine-geleide MR blokkade moeten evalueren.

Module Behandeling Cushing
Het is onduidelijk wat de rol is van chirurgie bij patiënten met een ACTH-onafhankelijk syndroom van Cushing op basis van bilaterale bijniervergroting. Bovendien is het niet duidelijk of het verwijderen van de grootste bijnier of bilaterale extirpatie de voorkeur heeft indien de patiënt in aanmerking komt voor een chirurgische behandeling.

Module Autonome cortisol (hyper)secretie (subklinische Cushing)
Wat zijn de voor- en nadelen van chirurgie vergeleken met een afwachtend beleid in patiënten met subklinisch Cushing's syndroom op cardiovasculaire events, diabetes en osteoporose?

Module Behandeling feochromocytoom

- Het is onduidelijk wat de toegevoegde waarde van preoperatieve alfablokkade voor een feochromocytoomresectie is en eventueel voor welke groep patiënten dit bijdraagt. De literatuur is van lage kwaliteit met een hoge kans op selectionbias, een gerandomiseerde studie zou uitkomst bieden
- Het is onduidelijk of er een verschil in opname duur (op een bewaakte afdeling) is tussen wel of geen preoperatieve alfablokkade

Module Expertisecentrum ACC

Er is geen goede definitie te maken van hoog- of laagvolume centrum voor adrenocorticaal carcinoom.
Deelname aan klinische en basale studies is, in samenwerkingsverband in Nederland en met Europa, noodzakelijk om kennislacunes over ontstaan en diagnostische en met name therapeutische opties te onderzoeken.

Module Biopsie bij ongedefinieerde retroperitoneale massa

Wat is de plaats van biopsie in het diagnostisch traject in het diagnostisch traject bij patiënten met een ongedefinieerde retroperitoneale massa mogelijk uitgaande van de bijnier?
Zoekvraag: What is the diagnostic performance of CT guided biopsy in patients with an atypical retroperitoneal mass in or near the adrenal gland which has not been diagnosed with adequate certainty by non-invasive imaging and laboratory tests? And what are the complications, including the risk of tumor seeding?

Module Behandeling bijniermetastasen

- Mochten chirurgie en hoge-dosis bestraling niet beschikbaar zijn in het eigen centrum, dan moet het duidelijk zijn voor artsen/verwijzers en patiënten, in welke centra ze wel toegang kunnen krijgen tot een ervaren team. Op dit moment is er geen transparante kennis voorhanden om te weten welke centra deze ervaring in huis hebben, hoeveel ervaring centra hebben en wat hun resultaten zijn. Er bestaat dus geen register van “approved” centra en er bestaan geen kwaliteitseisen.
    - Mogelijke onderzoeksvraag: Aan welke kwaliteitseisen moet een centrum voldoen voor het aanbieden van chirurgie of stereotactische radiotherapie als behandeling van bijniermetastasen?
- Er zijn data die lijken te suggereren dat patiënten met longmetastasen van colorectaal carcinoom een lagere lokale controle hebben dan verwacht na stereotactische radiotherapie (o.a. Sheikh, 2022): er is nog niet genoeg bewijs om vast te stellen of hetzelfde geldt voor bijniermetastasen van colorectale origine (of misschien van bepaalde andere soorten van primaire tumoren). Er zijn meer data nodig om deze vraag te beantwoorden. Mocht het niet mogelijk zijn om de hoogste bestraling dosis te gebruiken dan kan het volgende overwogen worden: (1) is er elders een bestraling techniek beschikbaar die misschien een verschil kan maken in haalbare dosis?; (2) is een operatie te overwegen (in medisch en technisch operabele laesies met hoge kans R0 resectie)?
    - Mogelijke onderzoeksvraag: Wat zijn de relaties tussen radiotherapeutische parameters en klinische uitkomsten van patiënten met bijniermetastasen die behandeld worden met SBRT?
- Er is geen data voor een economische vergelijking tussen chirurgie en stereotactische radiotherapie.
    - Mogelijke onderzoeksvraag: Wat is de kosteneffectiviteit van stereotactische radiotherapie in vergelijking met chirurgie als behandeling van bijniermetastasen?

- De huidige status van kennis biedt in principe een kans voor een gerandomiseerde studie tussen chirurgie en stereotactische radiotherapie voor medisch en technisch operabele (met hoge waarschijnlijkheid R0 resectie) bijniermetastasen; maar de historische ervaringen met RCTs tussen chirurgie en stereotactische radiotherapie pleiten ervoor de kans op succes niet te overschatten.
    - Mogelijke onderzoeksvraag: Wat zijn de (on)gunstige effecten van stereotactische radiotherapie in vergelijking met chirurgie bij de behandeling van bijniermetastasen?

Module Minimaal invasieve chirurgie

- Minder heterogeniteit in de studiepopulatie:
  P: Patiënten met een benigne bijniertumor
  I: Retroperitoneoscopische adrenalectomie
  C: Laparoscopische adrenalectomie
  O: Tijd tot volledig herstel (hervatting werk/sport), complicaties, opnameduur, conversie, postoperatieve pijn
- Een belangrijke kennislacune wordt gevormd door een gebrek aan prospectieve gerandomiseerde studies in homogene patiënten populaties van niet-maligne bijniertumoren met goed gedefinieerde eindpunten. Hierbij kan tijd tot herstel worden gedefinieerd als de tijd die de patiënt nodig heeft tot hervatting van werk/sport, registratie van opnameduur geschieden met gestandaardiseerde ontslagcriteria ter correctie van lokale usance en postoperatieve pijn te worden geregistreerd met VAS scores en/of pijnstilling gebruik met vermelding van medicatie en dosering.
- Een en ander is eventueel te combineren met een 3^{e} studie-arm om de rol van robotchirurgie bij minimaal invasieve bijnieroperaties te onderzoeken:
  P: Patiënten met een benigne bijniertumor
  I: Robot adrenalectomie
  C: Minimaal invasieve adrenalectomie (laparoscopisch/retroperitoneoscopisch)
  O: Tijd tot volledig herstel (hervatting werk/sport), complicaties, opnameduur, conversie, postoperatieve pijn

Module Genetisch testen en chirurgisch beleid

Hoe wordt het beloop van de ziekte beïnvloed als het operatieve beleid wordt aangepast naar aanleiding van een erfelijke oorzaak bij een patiënt van wie eerder niet bekend was dat hij erfelijk belast is?

Module Pathologieverslag

Er is geen systematische zoekvraag gedaan voor dit onderdeel. Niettemin kunnen op basis van de geraadpleegde literatuur een aantal kennislacunes worden geformuleerd:

1. Welke diagnostische en prognostische waarde hebben individuele elementen van de ICCR dataset?
2. Welke kenmerken kunnen het klinisch gedrag van pediatrische ACC en PPGL voorspellen?
3. Welke bijdrage kunnen moleculaire kenmerken leveren aan de diagnostiek (onderscheid tussen benigne en maligne bijnierschortumoren) en aan de predictie en prognose van ACC en PPGL?

Module Radiologieverslag

Verdere grote prospectieve studies op het gebied van navolging van de richtlijnen rondom bijnier incidentalomen zijn nodig volgens de werkgroep. Hierin dient met name te worden

gekeken naar de mate van doorverwijzing en follow-up. Tevens zou gekeken kunnen worden of het gebruik van standaard terminologie ook daadwerkelijk toeneemt in radiologische verslaglegging. Additioneel is interessant te onderzoeken in hoeverre deze (follow-up) strategieën volgens bestaande algoritmen kosteneffectief zijn en in hoeverre volgens gestandaardiseerd radiologisch rapport terecht onderscheid wordt gemaakt tussen benigne en maligne entiteiten. De volgende kennislacunes kunnen worden geformuleerd:

1. Wat is de invloed van navolging van de richtlijnen rondom beeldvorming en verslaglegging van bijnier incidentalomen op de mate van doorverwijzing en follow-up?
2. In hoeverre zijn de (follow-up) strategieën volgens bestaande algoritmen kosteneffectief?
3. Wat is het effect van standaardisatie van het radiologisch rapport op onderscheid maken tussen benigne en maligne entiteiten?

Module Follow-up

Prospectief onderzoek naar het ontstaan van een tweede primair feochromocytoom bij genetisch belaste patiënten is gewenst (valt buiten bestek van deze richtlijn).

Module Aandacht bijnierschorsinsufficiëntie

Meer onderzoek naar risicofactoren is gewenst met gevalideerde predictiemodellen.
P: Patiënten na unilaterale adrenalectomie in geval van bijnier incidentaloom
I: Gevalideerd predictiemodel dat bijnierinsufficiëntie kan voorspellen
C: Geen model (normale zorg)
O: Overleving, voorspellende waarde van het model

Bijlage 2 – Implementatieplan

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Diagnostiek bijnier incidentaloom	< 1 jaar	Geen	Infrastructuur is aanwezig Doelgroep informeren	Geen	Geen, afstemmen binnen doelgroepen	Individuele behandelaar	Geen
Diagnostiek Morbus Conn	< 1 jaar	Geen	Infrastructuur is aanwezig Doelgroep informeren	Niet in ieder centrum is AVS beschikbaar	Verwijzing naar centrum waar AVS beschikbaar is kan noodzakelijk zijn.	Individuele behandelaar	Geen
Behandeling Morbus Conn	< 1 jaar	Geen	Bereiken doelgroep, informeren	Gebrek aan expertise	Aanwenden expertise, behandeling in gespecialiseerde centra	Diverse betrokken partijen in het zorgveld (wetenschappelijke verenigingen, organisaties)	Geen
Behandeling Cushing	< 1 jaar	Geen	Bereiken doelgroep, informeren	Geen	Geen	Geen	Geen
Autonome cortisol (hyper)secretie (subklinische Cushing)	< 1 jaar	Geen	Bereiken doelgroep, informeren	Gebrek aan expertise	Geen	Individuele behandelaar	Geen
Feochromocytoom	< 1 jaar	Mogelijke daling in kosten	Expertise	Gebrek aan expertise	Geen	Behandelaren	Multidisciplinaire afstemming over hoe met

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
							blokken om te gaan is gewenst binnen elk centrum (anesthesioloog, chirurg, internist)
Expertise centrum ACC	< 1 jaar	Geen	Geen	Geen	Geen	Geen	Geen
Biopsie bij ongedefinieerde retroperitoneale massa	< 1 jaar	Verwaarloosbaar	Geen	Geen	Geen	Geen	Geen
Behandeling bijniermetastasen	< 1 jaar	Geen	Infrastructuur dient aanwezig te zijn	Gebrek aan lokale expertise	Verwijzing naar expertise centrum kan noodzakelijk zijn	N.v.t.	
Minimaal invasieve chirurgie	< 1 jaar	Geen	Expertise m.b.t. minimaal invasieve techniek	Gebrek aan expertise en vaardigheden	Nascholing, proctoring techniek	Individuele behandelaar	
Genetisch testen en chirurgisch beleid	<1 jaar	Geen	Aanpassen zorgproces	geen	Geen	Klinisch geneticus	-
Pathologieverslag	<1 jaar	geen	Bereiken doelgroep	Acceptatie richtlijn	Verspreiden via expertise groep endocriene pathologie (EEP)	Voorzitters van EEP	Geen

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
					van NVVP		
Radiologieverslag	< 1 jaar	Geen	Bereiken doelgroep	Gebrek aan expertise	Nascholing, richtlijn verspreiden via NVVR	Adherentie door verslagleggend arts	Geen
Follow-up	< 1 jaar	Geen	Geen	Geen	Geen	Geen	Geen
Aandacht bijnier insufficiëntie	< 1 jaar	Geen	Geen	Geen	Geen	Geen	Geen

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

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

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

Bijlage 3 – Verslag invitational conference

Notulen invitational conference richtlijn *Bijniertumoren*

Datum: woensdag 22 september 2021
Tijd: 17:00 – 18.30 uur
Plaats: via Zoom

Aanwezig: Menno Vriens (NVvH, voorzitter), Schelto Kruijff (NVvH, voorzitter), Hans Langenhuijsen (NVU), Harm Haak (NIV), Max Dahele (NVRO), Bernadette van Nesselrooij (VKGN), Diana Kwast-Hoekstra (Bijniervereniging NVACP, patiëntvertegenwoordiger), Rebecca Steenaard (IKNL), Eline de Heus (IKNL), Hinke Nagtegaal (NAPA, vakgroep Interne Geneeskunde), Gabriëla Cuperus (Belangenvereniging Von Hippel-Lindau)

Ondersteuning Kennisinstituut: Anja van der Hout, Niels Elbert

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1) Opening
De voorzitters van de richtlijn, Menno Vriens en Schelto Kruijff, heten iedereen welkom en openen de bijeenkomst.

2) Kennismaking
Alle aanwezigen stellen zich kort voor en geven aan welke partij zij vertegenwoordigen.

3) Toelichting doel bijeenkomst en proces richtlijnontwikkeling
Anja licht het doel van de bijeenkomst toe en geeft uitleg over het proces van de richtlijnontwikkeling aan de hand van een presentatie (bijlage I).

4) Impact probleem bijniertumoren en de richtlijn
Menno en Schelto lichten de impact van bijniertumoren toe en wat de richtlijn daarin kan betekenen.

De aanleiding voor de richtlijn is bestaande praktijkvariatie op gebied van diagnostiek en chirurgische behandeling van bijniertumoren. De richtlijn is daarom erg gewenst in het veld.

5) Concept afbakening en inhoudelijke hoofdlijnen richtlijn 'Bijniertumoren' en rondvraag knelpunten

Afbakening
De richtlijn beperkt zich tot bijniertumoren die in potentie chirurgisch behandeld kunnen worden, inclusief bijniermetastasen. Ook wordt aandacht besteed aan hormoontherapie na chirurgische behandeling bij patiënten met hormoongevoelige bijniertumoren. Viriliserende tumoren worden beschouwing gelaten.

Er wordt gevraagd of de richtlijn alleen voor volwassenen wordt geschreven. De patiëntvertegenwoordigers geven aan dat zij het belangrijk vinden dat de richtlijn ook betrekking heeft op kinderen. Hier zijn de aanwezigen het mee eens. Dit wordt aan de afbakening toegevoegd.

<u>Conceptraamwerk</u>
Het conceptraamwerk wordt uitgebreid besproken, waarbij Schelto discussie leidt. Per module wordt besproken of deze relevant is en wat het precieze knelpunt is. Bij een aantal modules worden uitgangsvragen opgesteld.

Rondvraag knelpunten

Er wordt een knelpunt ingebracht over genetisch onderzoek. De aanwezigen vinden dit een belangrijk knelpunt.
De vraag daarbij is ‘Wat is de rol van genetisch onderzoek in het diagnostische proces en bij de keuze voor bepaalde operatiestrategie bij feochromocytoom, adrenocorticaal carcinoom en incidentaloom?’.

Er wordt ook een knelpunt ingebracht over nazorg. De patiëntvertegenwoordiger geeft aan dat patiënten behoefte hebben aan meer houvast in het nazorgtraject, dat bij voorkeur afgestemd wordt met de verpleegkundig specialisten. Dit punt wordt meegenomen in de module over de follow-up.

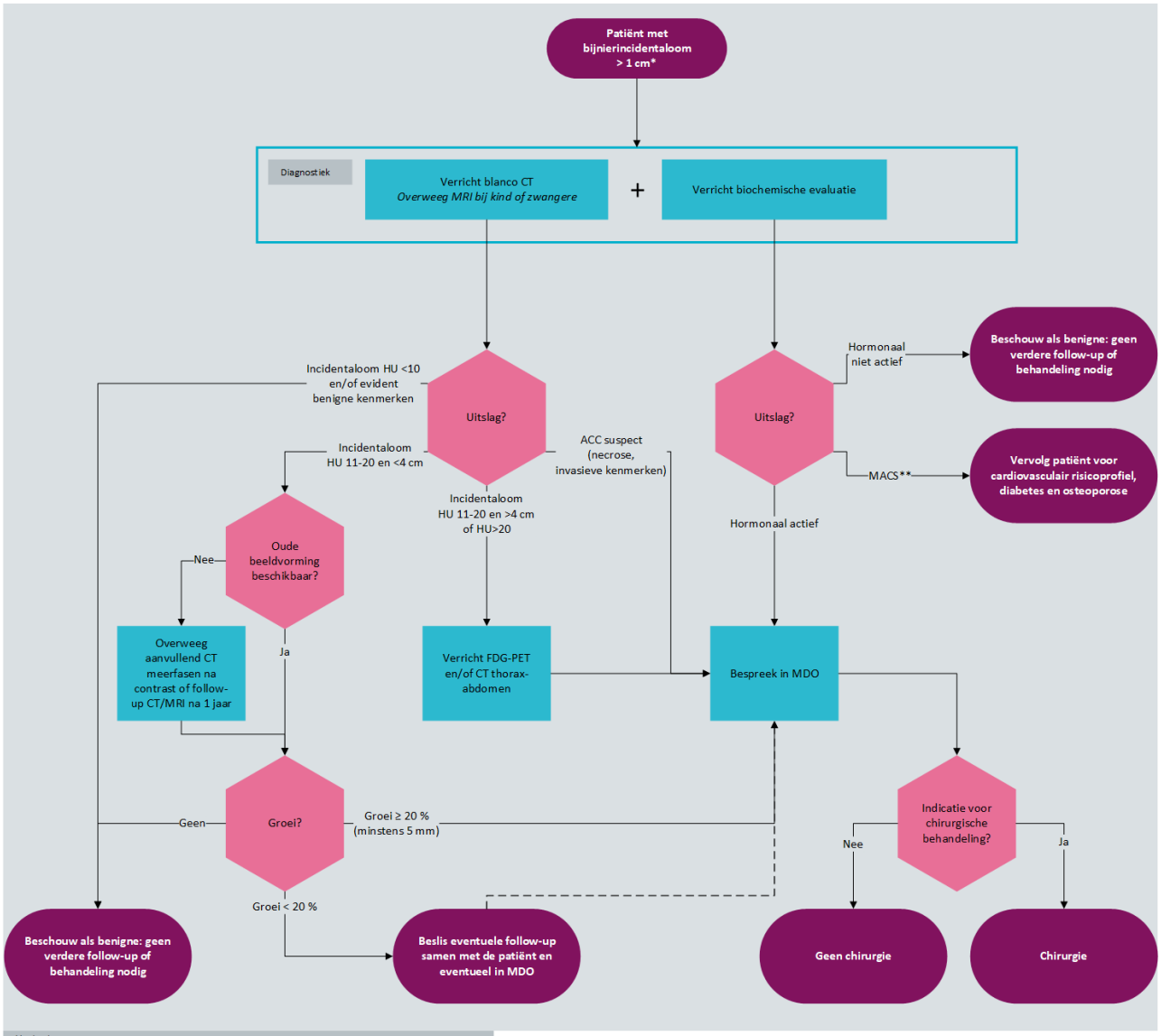
6) Vervolgafspraken

De werkgroep (nu deels aanwezig) zal in volgende vergaderingen de input vanuit deze bijeenkomst meenemen en het raamwerk verder definiëren. Niet alle uitgangsvragen zullen kunnen worden uitgewerkt binnen de beschikbare tijd en budget. Er zal nog verder worden geprioriteerd.

Er wordt een beknopt verslag gemaakt van deze bijeenkomst. Als het raamwerk is aangepast door de werkgroep zullen deze stukken worden toegestuurd aan de aanwezigen van vanavond. Iedereen krijgt dan nog kort de mogelijkheid om te reageren. Dit verslag wordt ook bij als bijlage bij de richtlijn gepubliceerd op de richtlijnendatabase.

Bijlage 4 – Stroomschema Diagnostiek

(bijlage bij alle modules)



Voetnoten:
* Dit stroomschema is van toepassing wanneer de patiënt geen bekende maligniteit heeft.
** MACS: patiënt zonder duidelijke klinische kenmerken van het Cushing syndroom, waarvan de cortisol concentratie na een 1 mg Dexamethason overnight suppressie test boven de 50 nmol/L is.

Nederlandse Vereniging voor Heelkunde
Initiatiefnemende vereniging

NB1: Dit stroomschema hoort bij de module 'Diagnostiek' van de richtlijn 'Diagnostiek en behandeling van Bijniertumoren'. Lees altijd de overwegingen en aanbevelingen van de betreffende module voor nuances, eventuele afwijkende situaties en extra achtergrondinformatie.

NB2: Betrek de patiënt bij de besluitvorming.

Federatie Medisch Specialisten
Ontwikkeld door het Kennisinstituut van de Federatie Medisch Specialisten