Conceptrichtlijn Herziening Hepatocellulaircarcinoom

INITIATIEF
Nederlandse Vereniging van Maag-Darm-Leverartsen

IN SAMENWERKING MET
Nederlandse Internisten Vereniging
Nederlandse Vereniging voor Heelkunde
Nederlandse Vereniging voor Nucleaire Geneeskunde
Nederlandse Vereniging voor Pathologie
Nederlandse Vereniging voor Radiologie
Nederlandse Vereniging voor Radiotherapie en Oncologie
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Colofon

CONCEPTRICHTLIJN HERZIENING HEPATOCELLULAIRCARCINOOM

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Inhoudsopgave

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Startpagina – titel van de richtlijn of module

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Verantwoording

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:	(Noteer hier de belangrijkste wijzigingen als de module een herziening betreft)
Herbevestiging:	(datum) (onderbouwing waarom module niet herzien is)
Regiehouder(s):	(Betreffende verenging)

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 Stichting Kwaliteitsgelden Medisch Specialisten (SKMS).

De financier heeft geen enkele invloed gehad op de inhoud van de richtlijnmodule.

Samenstelling werkgroep

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

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.

Achternaam werkgroeplid	*Hoofdfunctie*	*Nevenwerkzaamheden*	*Persoonlijke financiële belangen*	*Persoonlijke relaties*	*Extern gefinancierd onderzoek*	*Intellectuele belangen en reputatie*	*Overige belangen*
De Man (vz.)	Hoogleraar Hepatologie, Erasmus MC Rotterdam	Geen	Geen	Geen	Geen	Geen	Geen
Haj Mohammad	Internist-oncoloog, Universitair Medisch Centrum Utrecht	Penningmeester Dutch Upper GI Cancer (DUCG), onbetaald Wetenschappelijke raad Dutch Heptocellular and Cholangiocarcinoma group (DHCG), onbetaald Lid richtlijn galwegcarcinoom, onbetaald. De DHCG is een gemeenschappelijk initiatief van Nederlandse medisch specialisten om de krachten in de strijd tegen lever- en galwegkanker te bundelen	Geen	Geen	Geen	Lid wetenschappelijke raad Dutch Hepato and Cholangio Carcinoma Group(DHCG)	Geen
Burgmans	Sectiehoofd interventie radiologie LUMC	Voorzitter Nederlandse Vereniging Interventieradiologie Bestuurslid Nederlandse Vereniging voor Hepatologie Voorzitter Normendocument interventieradiologie Lid Wetenschappelijke Commissie Interventieradiologie Allen onbetaald	Geen	Geen	PROMETHEUS studie, subsidie KWF, project leider HORA EST HCC studie, subsidie ZonMW, MLDS, Health Holland, project leider	Geen	Geen

Lam	Nucleair geneeskundige, UMC Utrecht	Geen	Geen	Geen	Terumo, Quirem Medical en Boston scientific leveren financiële steun aan wetenschappelijke projecten	Geen	Het UMC Utrecht ontvangt royalties en milestone payments van Terumo/Quirem Medical
Franken	Verpleegkundig Specialist Levertumoren Afdeling HPB - transplantatie chirurgie Erasmus MC	Geen	Geen	Geen	Geen	Geen	Geen
Verheij	Hoogleraar hepatopancreatobiliaire Pathologie aan de Universiteit van Amsterdam Klinisch Patholoog Amsterdam UMC, Amsterdam	lid medische adviesraad NLV (onbezoldigd)	Geen	Geen	Geen	Geen	Geen
Sprengers	MDL-arts Erasmus MC	Geen	Geen	Geen	Ik doe translationeel onderzoek met als doel behandeling van patiënten met een HCC te verbeteren. Daarbij wordt soms samengewerkt met famaceutische partijen die producten ontwikkelen die hieraan bij kunnen dragen. Te allen tijde betreft dit objectief wetenschappelijk onderzoek zonder winstoogmerk.	Geen	Geen
Van Vilsteren	MDL-arts UMCG 0,9 fte	Geen	Geen	Geen	Geen	Geen	Geen
Takkenberg	Maag- Darm Leverarts met specifiek aandachtsgebied leverziekten. Sinds 1-4-2015 in deinst van het Amsterdam UMC, locatie AMC.	Geen	Betaald adviesschap: Swedish Orphan Biovitrum BV/SRL (Sobi) Norgine bv.	Geen	Ik ben PI van de PEARL studie. Dit is een dubbelblind gerandomiseerde studie bij patiënten die een transjugulaire intrahepatische portosysthemische shunt (TIPS)	Secretaris Dutch Hepatocellular and cholangiocarcinoma Group (DHCG) Voorzitter werkgroep portale hypertensie	Geen

					krijgen. Patiënten worden gerandomiseerd tussen profylactisch lactulose en rifaximin versus lactulose en placebo. Doel is het voorkomen van post-TIPS hepatische encafalopathie (EudraCT-nummer 2018-004323-37). Deze studie wordt gefinancierd door ZonMW en ondersteund door Norgine. Zij leveren de rifaximin en placebo tabletten.	van de Nederlandse Vereniging voor Hepatologie (NVH). Voorzitter commissie ter organisatie van de Dutch Liver Week. Bestuurslid NVH.	
Van Erpecum	MDL-arts UMC Utrecht	Associate Editor European Journal of Internal Medicine (onbetaald) Editorial Board Clinics and Research in Hepatology and Gastroenterology (onbetaald) Editorial Board Biochimica Biophysica Acta, Molecular and Cell Biology of Lipids (onbetaald) Lid Medisch Ethische Toetsingscommissie UMC (onbetaald)	Geen	Geen	Geen	Geen	Geen
Willemssen	Abdominaal Radioloog Erasmus MC Rotterdam	Bestuurslid abdominale sectie NVvR (onbetaald)	Geen	Geen	Geen	Geen	Geen
Méndez Romero	Staflid afdeling radiotherapie in het Erasmus MC	Als staflid in ee adademisch ziekenhuis ben ik in loondienst van het ErasmusMC	Geen	Geen	Geen	Geen	Geen
Tjwa	MDL arts / hepatoloog	Geen	Geen	Geen	Geen	Geen	Geen
Braat	chirurg LUMC	Geen	Geen	Geen	Geen	Geen	Geen

Nijkamp	Chirurg Universitair Medisch Centrum Groningen	Geen	Geen	Geen	Geen	Geen	Geen
Willemse	Directeur Nederlandse Leverpatiënten Vereniging	* Bestuurslid Liver Patients International (onbetaald) * Bestuurslid ERN Rare Liver (onbetaald)	Geen	Geen	Geen	Geen	Geen
IJzermans	Hoofd HPB & Transplantatiechirurgie Erasmus MC	-	Niet van toepassing	Nee	Niet van toepassing	Niet van toepassing	Nee
Vos, de - Geelen	* Internist - Medisch Oncoloog Maastricht UMC+ * Secretaris DHCG - Landelijke werkgroep HCC en BTC	Has served as a constultant for Amgen, AstraZeneca, MSD, Pierre Fabre and Servier and has received institutional research funding from Servier	Has served as a constultant for Amgen, AstraZeneca, MSD, Pierre Fabre and Servier and has received institutional research funding from Servier. Geen directe financiële belangen in een farmaceutisch bedrijf	Geen	* Servier: Microbioomonderzoek - Projectleider * MLDS: Keuzehulp alvleesklierkanker - Projectleider	Geen	Geen
Hoek, van	* Hoogleraar Hepatologie, Universiteit Leiden * MDL-arts, medisch hoofd levertransplantatie en hepatologie, afd MDL, LUMC Leiden * Lid managementteam transplantatie afdeling LUMC, Leiden	* Norgine Pharma - patient voorlichtingsmateriaal maken, onder andere podcast - betaald * Norgine Pharma - farmaco-economische analyse - betaald * Sandoz Pharma - implementatie DBS monitoring immunsuppressie - betaald (lumc) * Astellas Pharma -	Geen	Nee	* Roche - Piranga Studie (hepatitis B) - Projectleider * ZonMW -TAILOR studie (auto-immuun hepatitis) - Projectleider * Takeda (Arrowhead) - AROOAT studie (alfa-1-anti trypsine deficientie) - Projectleider * Chiesi - MOTTO studie (tacrolimus na levertransplantatie) - Projectleider * Dicerna - Studie naar alfa-1-anti trypsine deficientie) -	Geen	Nee

		optimaliseren levertransplantaties database - betaald (aan lumc) * Chiesi Pharma & ZonMW - controlled trial auto-immuun hepatitis (betaald aan lumc)			Projectleider * Sandoz - Implementatie DBS voor immunsuppressie monitoring - Projectleider * Nutricia - voedingsonderzoek bij leverziekte/-transplantatie - Projectleider		
Delden, van	Radioloog, Amsterdam UMC	Voorzitter DHCG	Geen	Geen	Geen	Geen	Geen
Doukas	Universitair Medisch Specialist, Patholoog, Afdeling Pathologie Erasmus MC, Rotterdam	Geen	Niet van toepassing	Niet van toepassing	Niet van toepassing	Niet van toepassing	Niet van toepassing
Coenraad	Associate professor, MDL arts Leids Universitair Medisch Centrum (1.0 fte) Visitng professor afd Hepatologie KU Leuven Belgie (onbezoldigd)	Nevenfuncties: -Bestuursvoorzitter Nederlandse Vereniging voor Hepatologie (onbetaald) -United European Gastroenterology Summer School Course Director (onbetaald) -Lid Landelijk Overleg Levertransplantatie (onbetaald) -Associate Editor van peer-reviewed internationaal tijdschift Liver International (hiervoor ontvang ik jaarlijks plm 2000 Euro onkostenvergoeding) -Voorzitter van Nederlands richtsnoer Lever Transplantatie voor HCC (onbetaald) -Bestuurslid Dutch	Niet van toepassing	Niet van toepassing	* Horizon2020 - EU Project id 945096. Title 'Novel treatment of acute-on-chronic liver failure using synergistic action of G-CSF and TAK-242 - Geen projectleider * 2020 MLDS grant - Gepersonaliseerde blended coaching ter bevordering van een gezonde leefstijl bij mensen met (risico op) leververvetting - Geen projectleider * 2020 Dutch Cancer Society - Prospective multicenter study of the relationship between safety margin and recurrent tumor after thermal ablation in patients with liver cancer - Geen projectleider * 2019 Johanna Zaaijer Fund - Role of endothelial cells in pathogenesis of acute decompensation, acute on chronic liver failure and in liver regeneration - Projectleider	Niet van toepassing	Niet van toepassing

		Hepatocellular Carcinoma Group (onbetaald) -2019-2022 2019 UEG National Societies Committee member, UEG education committee member (onbetaald)					
Erdmann	Chirurg AUMC	geen	geen	geen	AGEM - perfusie onderzoek (50K), rol als projectleider	geen	geen

Inbreng patiëntenperspectief

Er werd aandacht besteed aan het patiëntenperspectief door deelname van de afgevaardigde patiëntenvereniging Nederlandse Leverpatiëntenvereniging in de werkgroep. De afgevaardigde heeft meebeslist 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 Nederlandse Leverpatiëntenvereniging 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 geen substantiële financiële gevolgen zijn voor deze richtlijn, gezien het aantal patiënten kleiner is dan 5000.

De kwalitatieve raming volgt na de commentaarfase.

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 Hepatocellulaircarcinoom. De werkgroep beoordeelde de aanbeveling(en) uit de eerdere richtlijn Hepatocellulaircarcinoom op noodzaak tot revisie. Tevens zijn er knelpunten aangedragen door de deelnemende WV-en, de V&VN en de Nederlandse Leverpatiëntenvereniging.

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.

ethode literatuursamenvatting

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

Beoordelen van de kracht van het wetenschappelijke bewijs

De kracht van het wetenschappelijke bewijs werd bepaald volgens de GRADE-methode. GRADE staat voor 'Grading Recommendations Assessment, Development and Evaluation' (zie http://www.gradeworkinggroup.org/). De basisprincipes van de GRADE-methodiek zijn: het benoemen en prioriteren van de klinisch (patiënt) relevante uitkomstmaten, een systematische review per uitkomstmaat, en een beoordeling van de bewijskracht per uitkomstmaat op basis van de acht GRADE-domeinen (domeinen voor downgraden: risk of bias, inconsistentie, indirectheid, imprecisie, en publicatiebias; domeinen voor upgraden: dosis-effect relatie, groot effect, en residuele plausibele confounding).

GRADE onderscheidt vier gradaties voor de kwaliteit van het wetenschappelijk bewijs: hoog, redelijk, laag en zeer laag. Deze gradaties verwijzen naar de mate van zekerheid die er bestaat over de literatuurconclusie, in het bijzonder de mate van zekerheid dat de literatuurconclusie de aanbeveling adequaat ondersteunt (Schünemann, 2013; Hultcrantz, 2017).

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

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

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

Overwegingen (van bewijs naar aanbeveling)

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

Formuleren van aanbevelingen

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

In de GRADE-methodiek wordt onderscheid gemaakt tussen sterke en zwakke (of conditionele) aanbevelingen. De sterkte van een aanbeveling verwijst naar de mate van zekerheid dat de voordelen van de interventie opwegen tegen de nadelen (of vice versa), gezien over het hele spectrum van patiënten waarvoor de aanbeveling is bedoeld. De sterkte van een aanbeveling heeft duidelijke implicaties voor patiënten, behandelaars en beleidsmakers (zie onderstaande tabel). Een aanbeveling is geen dictaat, zelfs een sterke aanbeveling gebaseerd op bewijs van hoge kwaliteit (GRADE-gradering HOOG) zal niet altijd van toepassing zijn, onder alle mogelijke omstandigheden en voor elke individuele patiënt.

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

Organisatie van zorg

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

Commentaar- en autorisatiefase

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

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Module 1 Surveillance Hepatocellulaircarcinoom

Uitgangsvraag

Wat is de waarde van de MRI-scan voor surveillance bij patiënten met een verhoogd risico op hepatocellulair carcinoom?

Inleiding

Surveillance voor Hepatocellulaircarcinoom (HCC) wordt gedaan bij patiënten met een verhoogd risico op deze maligniteit. Meta-analyses en onderzoek in de Nederlandse setting laten zien dat surveillance geassocieerd is met HCC detectie in een vroeger stadium, vaker toepassen van curatieve therapie, en een betere overleving (Singal, 2022; Van Meer, 2015). In Nederland komen patiënten met levercirrose en patiënten met hepatitis B zonder cirrose, maar met andere risicofactoren (familiaire belasting met HCC, Chinese man ouder dan 40 jaar, Chinese vrouw ouder dan 50 jaar, Sub-Sahara Afrikaan ouder dan 20 jaar) in aanmerking voor surveillance. De bedoeling is patiënten in een nog curatief te behandelen stadium (BCLC-0 of BCLC-A), te detecteren.

Surveillance wordt meestal verricht met echografie (al dan niet in combinatie met alfafoetoproteïne) elke zes maanden. De sensitiviteit voor detectie in een curatief te behandelen stadium is met alleen echografie 45 procent en met echografie in combinatie met alfafoetoproteïne (AFP) 63 procent (Tzartzeva, 2018). Tevens is er kans op schade door fout positieve uitslagen (specificiteit 92 procent bij alleen echografie, 84 procent bij combinatie echografie en AFP). Wellicht dat Magnetic Resonance Imaging (MRI) een hogere sensitiviteit en specificiteit heeft voor detectie van HCC in een curatief te behandelen stadium.

Search and select

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

What is in patients with an indication for HCC surveillance, the diagnostic value of Magnetic Resonance Imaging (MRI) scan in comparison with ultrasound (US) with or without alpha fetoprotein, and what are the percentages curatively treated patients, overall and recurrence-free survival and the costs for MRI-based detection when compared with ultrasound-based detection?

P: patients with cirrhosis and patients with hepatitis B without cirrhosis;
I: MRI-Scan;
C: ultrasound;
R: diagnosis according to the American Association for the Study of Liver Disease (AASLD) criteria (Marrero, 2018) or the European Association for the Study of the Liver (EASL) criteria (European Association for the Study of the Liver, 2018);
O: diagnostic value for (very) early-stage HCC and diagnostic value for all stage HCC (sensitivity, specificity, positive predictive value, negative predictive value), (very) early-stage detection rates, overall survival, recurrence-free survival, costs.
Timing and setting: Patients who are at risk for developing HCC are under surveillance every six months in the hospital.

P: patients with cirrhosis and patients with hepatitis B without cirrhosis;
I: MRI-scan;
C: Ultrasound with Alpha Fetoprotein;

R: diagnosis according to the American Association for the Study of Liver Disease (AASLD) criteria (Marrero, 2018) or the European Association for the Study of the Liver (EASL) criteria (European Association for the Study of the Liver, 2018);

O: diagnostic value for (very) early-stage HCC and all stage HCC (sensitivity, specificity, positive predictive value, negative predictive value), (very) early-stage detection rates, overall survival, recurrence-free survival, costs).
Timing and setting: Patients who are at risk for developing HCC are under surveillance every six months in the hospital.

Relevant outcome measures

Regarding the surveillance setting in the Netherlands, the guideline development group considered sensitivity, negative predictive value and very early or early BCLC stage detection rate as *critical outcome measures* for decision making and specificity, positive predictive value, overall survival, recurrence-free survival and costs as *important 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.

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

- Sensitivity: No definition.
- Negative predictive value: No definition.
- Specificity: No definition.
- Positive predictive value: No definition.
- (Very) early-stage detection rate: No definition.
- Overall survival: An effect of surveillance resulting in either >5% or >3% combined with HR<0.70 was considered clinically relevant (BOM, 2018).
- Recurrence-free survival: An effect of surveillance resulting in HR<0.70 was considered clinically relevant (BOM, 2018).
- Costs: No definition.
-

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched for relevant search terms until 9 February 2022. The detailed search strategy is depicted under the tab Methods. The search did not include RCT's.

The systematic literature search resulted in 493 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 and comparator test had to be as defined in the PICRO.
- The index test and comparator test had to be directly compared in the same study.
- One or more reported outcomes had to be reported as defined in the PICRO.
- Research type: Systematic review, Randomized Controlled Trial and observational cohort study.
- Articles written in English or Dutch.

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

Results

Eight studies were included in the analysis of the literature. Important study characteristics and results of the diagnostic test accuracy studies are summarized in evidence table 1.1. Important study characteristics and results of the cost-effectiveness studies are summarized in evidence table 2. The assessment of the risk of bias of the diagnostic test accuracy studies is summarized in risk of bias table 1. The assessment of the risk of bias of the cost-effectiveness studies is summarized in risk of bias table 1.2.

Summary of literature

Description of studies

Diagnostic test accuracy studies

Kim (2016) performed a prospective, single center, cohort study in South-Korea. Patients who were twenty years or older with presence of cirrhosis with an estimated annual HCC risk of more than 5% (risk was estimated by using a model, if risk index was greater than 2.33 that was estimated to correspond to an annual risk of developing HCC of more than 5%), Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and no previous history or current suspicion of HCC, were included. In total, 407 patients were included in this study. Median age was 56 years, 43 percent was female and in 71 percent, the Hepatitis B virus was the cause of the liver disease. 78 percent of the patients had Child-Pugh class A and 21 percent had Child-Pugh class B.

Patients were evaluated by three rounds of screening tests with paired ultrasound (US) and gadoxetic acid-enhanced MRI at six months intervals. The index test was the liver MRI performed with 1.5-T scanner and gadoxetic acid (Primovist®) was administered at a dose of 0.025 mmol per kilogram. The positive screening criterium was category five on a five-point scale for MRI indicating the likelihood of HCC. The comparator test was an ultrasound. The positive screening criterium was category four of a four-point standardized scale for US indicating the likelihood of HCC. Reference tests and confirmation of HCC was based on results of histologic examination and/or typical CT images with nodule of more than one centimeter with arterial hypervascularity and portal/delayed-phase washout as recommended by practice guidelines. When MRI or US examination detected a nodule scored as category five or four, reference testing with CT-scan was performed within three months. Cases that were suspicious for HCC on CT imaging underwent biopsy whenever possible. At six months after the last screening round, all study patients were followed-up with dynamic CT-scan.

During the study with median follow-up of 1.5 years, 43 patients (11%) were diagnosed with HCC.

Kim (2016) reported detection rate for any HCC (sensitivity), detection rate for very-early and early-stage HCC (sensitivity), as well as specificity, false-negative rate, false-positive rate and positive predictive value as diagnostic test accuracy outcomes.

Park (2020) conducted a retrospective analysis, using the prospectively collected data from the study of Kim (2016) mentioned above. Selection criteria were as reported by Kim (2016). After the first surveillance round, patients were excluded if they withdraw from the study or died without subsequent follow-up information. In total, 382 patients were included in this study. Median age was 56 years, 43% was female and in 72%, the Hepatitis B virus was the cause of the liver disease.

Patients were evaluated by three rounds of surveillance with ultrasound and non-enhanced MRI at six months intervals. The index test was the liver MRI performed with 1.5-T scanner. The simulated non-enhanced MRI set consisted of axial DWI and T2WI. The positive screening criterium was a lesion of one centimeter or more with either diffusion restriction or mild to moderate T2 hyperintensity. The comparator test was ultrasound (US) examinations performed by board-certified abdominal radiologists using a convex probe (SC6-1, Supersonic Image SA). The positive screening criterium was one or more focal lesions of one centimeter or more on US that met one or more of the following criteria: 1) Discrete focal mass distinguishable from the adjacent parenchyma, 2) Peripheral low echoic halo, 3) Mosaic pattern, 4) Definite tumor thrombi visible on US.

The reference tests were dynamic CT scan, biopsy and/or subsequent surveillance round(s). Confirmation of HCC was based on results of histologic examination and/or typical CT images with nodules of more than one centimeter with arterial hypervascularity and portal/delayed-phase washout.

Park (2020) reported per-patients sensitivity, specificity, positive predictive value, negative predictive value and (very) early-stage detection rate as diagnostic test accuracy outcomes.

Park (2021) conducted a retrospective analysis, using prospectively collected data of the study of Kim mentioned above (2016). Selection criteria were identical to those of Kim (2016). After the first surveillance round, patients were excluded if they withdraw from the study or died without subsequent follow-up information. In total, 382 patients were included in this study. Study population characteristics were as reported by Park (2020).

Patients were evaluated by three rounds of screening tests. The CAA-approach consisted of a contrast MRI (CMRI) scan in the first round and abbreviated MRI (AMRI) scans in round two and three. The CMRI included T1-weighted imaging, DWI, T2WI and contrast-enhanced gadoxetic acid (Primovist®) T1-weighted imaging. The AMRI included DWI, T2WI and HBP imaging. Confirmation of HCC was based on LI-RADS classification. The AAA-approach consisted of abbreviated MRI (AMRI) scans in round one, two and three.

The reference test was as reported by Park (2020).

Park (2021) reported per-patients sensitivity, specificity and accuracy for round one, round two and three and in total and Park (2021) reported (very) early-stage detection rate.

Sutherland (2017) performed a prospective, single center, cohort study in Australia. Patients who were eighteen years or older with chronic liver disease and referred for hepatocellular carcinoma surveillance, were included. A total of 192 patients were included with median age of 58 years and 72 percent was male. The cause of the chronic liver disease was hepatitis B virus in 56 %, hepatitis C virus in 29% and alcohol in 11%.

The index test consisted of MRI-scan comprising respiratory-gated DWI. MRI lesions were considered suspicious if they had elevated signal on high b value DWI and were iso or hypointense to background liver on the ADC map.

The comparator test consisted of ultrasound. Lesions were considered suspicious if they were solid and not clearly focal fat infiltration or focal fat sparing.

The reference testing comprised arterial phase hyperenhancement followed by washout on either CT or MRI or histology (biopsy or resection). The confirmation of definite HCC was based on the AASLD guidelines. Any suspicious lesion was documented with respect to size, features and hepatic segment. Prior imaging was reviewed to aid in the diagnostic classification of the lesion. If lesion was new, further investigation was performed following the AASLR guidelines, being repeat imaging in three months by the modality that identified it for lesions under 10 mm and cross-sectional contrast-enhanced multiphase imaging with MRI or CT scan for new lesions of at least 10 mm.

During the study, six patients were diagnosed with HCC which results in an incidence of 3 percent.

The MRI was used as a replacement test for US. Sutherland (2017) reported sensitivity, specificity, positive predictive value and negative predictive value for MRI and US.

Cost-effectiveness studies

Kim (2019) designed a Markov model to compare the expected (incremental) effects, costs and quality adjusted life years (QALYs) between MRI and ultrasound, over a 20-year time horizon. The cohort consisted of 10,000 patients with compensated cirrhosis (Child-Pugh A) and a starting age of 50 years. Eleven health states were included in the model with a surveillance cycle length of six months. The annual HCC incidence rate was assumed to be 3% and costs and effectiveness were discounted at five percent. Costs were estimated from the viewpoint of the healthcare system. Kim (2019) reported life years, cost in US dollars, QALYs and the Incremental Cost Effectiveness Ratio (ICER) in US dollars per QALY.

Lima (2019) designed a Markov model to compare the expected (incremental) QALYs and techniques (US, CT, complete MRI and abbreviated MRI), regarding lifetime horizon. Because of the scope of our research question, only surveillance strategies of US compared with MRI are considered here. The cohort consisted of patients with compensated cirrhosis (Child-Pugh A) at a starting age of 50 years. The surveillance cycle length was six months. The HCC incidence rate was assumed to be 3% and costs and outcomes were discounted at 1.5%. Costs were estimated from the viewpoint of the healthcare system. Lima (2019) reported QALYs, incremental costs in Canadian dollars and QALYs, and ICER in Canadian dollars per QALY. The MRI and US surveillance strategies were evaluated for an maximal scenario (100 percent of the patients entered with Child-Pugh A and an assumed compliance rate of 100 percent) and for a conservative scenario (29 percent of the patients with Child-Pugh A and an assumed compliance rate of 52 percent).

Nahon (2022) designed a Markov model to compare the expected (incremental) effects and costs between MRI and ultrasound surveillance, over a 20-year time horizon. The cohort consisted of 10,000 patients with compensated cirrhosis (Child-Pugh A) and a starting age of 50 years. Fourteen health states were included in the model with a surveillance cycle length of 3months. The HCC incidence rate was assumed to be 3% and costs and effectiveness were discounted at 2.5%. Costs were estimated from the viewpoint of the healthcare system. Nahon (2022) reported discounted life years, costs in euros and ICER in euros per life year.

Tan (2021) designed a Markov model to compare the expected (incremental) costs and QALYs for three surveillance strategies: No surveillance, ultrasound and Non-contrast Enhanced MRI (NCEMRI), over a 40-year time period. The cohort consisted of 482,000 patients who were at risk for HCC with an average age of 40 years. The surveillance cycle length was 6 months. The annual HCC incidence rate for patients with alcoholic cirrhosis was

1.6%, for patients with chronic hepatitis C cirrhosis was 4% and for patients with NASH (with or without cirrhosis) 2.6% developed HCC annually. An estimated pooled transition probability of 1.1% was taken into account and costs and outcomes were discounted at 3%. Seven health states were included in the model. Costs were estimated from the viewpoint of the healthcare system. Tan (2021) reported incremental effects, incremental costs and ICER in dollars per QALY for the three surveillance strategies.

Results

Diagnostic accuracy for detection of (very) early-stage HCC (Table 1.1)

One study reported diagnostic accuracy of MRI and US for detection of (very) early-stage HCC (Kim ,2016). Results are presented in table 1.1.

Table 1.1 Diagnostic accuracy for detection of (very) early-stage HCC

Study	Diagnostic Modality	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Kim, 2016	Contrast-enhanced MRI	85%	97%	53%	99%
	US	27%	94%	16%	97%

Diagnostic accuracy for detection of HCC (all stages)

Four studies reported diagnostic accuracy of MRI and US for detection of HCC all stages (Kim, 2016; Park, 2020; Park, 2021; Sutherland, 2016). Regarding the diagnostic accuracy of the US, the studies of Park (2020) and Park (2021) used the data from the study of Kim (2016). Therefore, the diagnostic accuracy regarding US in these studies, is only reported for the study of Kim (2016). The results are presented in table 1.2.

Table 1.2. Diagnostic accuracy for detection of HCC (all stages)

Study	Diagnostic Modality	Sensitivity – HCC all stages	Specificity – HCC all stages	Positive predictive value – HCC all stages	Negative predictive value – HCC all stages
Kim, 2016	Contrast-enhanced MRI	86%	97%	54%	99%
	US	28%	94%	17%	97%
Park, 2020	Non-enhanced MRI	79%	98%	62%	99%
Park, 2021	Contrast-enhanced-Abbreviated MRI	91%	97%	46%	99%
	Abbreviated MRI	86%	96%	45%	99%
Sutherland, 2016	MRI	83%	98%	63%	99%
	US	100%	89%	23%	100%

Very early-stage detection rate

One reported (very) early-stage detection rate (Kim, 2016).

Kim (2016) reported very early-stage detection rate of 84.8 percent for MRI and 27.3 percent for US.

Overall survival

The study of Kim (2016) reported overall survival rate of patients with and without HCC. The estimated 3-year overall survival rate of patients with HCC was 86 percent and of patients without HCC it was 94.2 percent (HR 2.26 (95% CI 0.92-5.56)).

Recurrence-free survival

No studies reported recurrence-free survival.

Costs

Four studies performed a cost-effectiveness study (Kim, 2019; Lima, 2019; Nahon, 2022; Tan, 2021).

Three studies reported the costs per Quality-Adjusted Life Year (QALY) and Incremental Cost-Effectiveness Ratio (ICER) (Kim, 2019; Lima, 2019; Tan, 2021). The QALY is defined as an extra life year in good health where survival of an individual with their Health-Related Quality of Life (HRQoL) is combined (Whitehead, 2010). The ICER relate the costs of a treatment to its clinical benefit in terms of a ratio expression (dollars per quality adjusted life year) and therefore ICERs can be directly compared (Krummenauer, 2005)

The costs per QALY and ICER per QALY for MRI versus Ultrasound in the surveillance setting, are presented in table 1.3.

Table 1.3 Costs per QALY and Incremental Cost Effectiveness Ratios (ICER) per QALY

Study	Incidence HCC	Costs per QALY for MRI	Costs per QALY for US	ICER
Kim (2019)	5%	$10,191/QALY	$10,163/QALY	$10,721/QALY
	4%	$9,704/QALY	$9,424/QALY	$16,039/QALY
	3%	$9,182/QALY	$8,644/QALY	$25,202/QALY
	2%	$8,628/QALY	$7,819/QALY	$44,026/QALY
	1%	$8,038/QALY	$6,948/QALY	$101,586/QALY
Lima (2019)	3% - Optimal scenario	CAN$ 3,712/QALY	CAN$ 2,518/QALY	CAN$ 663,000/QALY
	3% - Conservative scenario	CAN$ 2,589/QALY	CAN$ 2,159/QALY	CAN$ 39,681/QALY
Tan (2021)	1.1%	$15,567/QALY	$2,117/QALY	$837,353/QALY
ICER: Incremental Cost-Effectiveness Ratio; $: US dollars; CAN$: Canadian dollars; €: Euro; QALY: Quality Adjusted Life Year; LYG: Life Year Gained				

The study of Nahon (2022) calculated costs per discounted Life Years (LY) and ICER per Life Years Gained (LYG) for MRI versus Ultrasound in the surveillance setting, which are presented in table 1.4.

Study	Incidence HCC	Costs per LY for MRI	Costs per LY for US	ICER per LYG
Nahon (2022)	3%	€7,744/LY	€7,517/LY	€15,477/LYG
	2%	€7,783/LY	€7,487/LY	€23,338/LYG
	1%	€7,942/LY	€7,545/LY	€47,194/LYG
ICER: Incremental Cost-Effectiveness Ratio; $: €: Euro; LY: Life Years; LYG: Life Years Gained				

Level of evidence of the literature

Sensitivity

The level of evidence regarding the outcome measure *sensitivity* was downgraded to very low GRADE because of study limitations (-1; risk of bias because of flow and timing), applicability (-1; bias due to indirectness because study population is not corresponding with population in the Netherlands) and number of included patients (-1; imprecision because confidence intervals may lead to different conclusions of the test's value).

Negative predictive value

The level of evidence regarding the outcome measure *negative predictive value* was downgraded to low GRADE because of study limitations (-1; risk of bias because of flow and timing) and applicability (-1; bias due to indirectness because study population is not

corresponding with population in the Netherlands). The level of evidence was therefore graded as low.

Specificity

The level of evidence regarding the outcome measure *specificity* was downgraded to low GRADE because of study limitations (-1; risk of bias because of flow and timing) and applicability (-1; bias due to indirectness because study population is not corresponding with population in the Netherlands).

Positive predictive value

The level of evidence regarding the outcome measure *positive predictive value* was downgraded to low GRADE because of study limitations (-1; risk of bias because of flow and timing) and applicability (-1; bias due to indirectness because study population is not corresponding with population in the Netherlands).

Very early-stage detection rate

The level of evidence regarding the outcome measure *Very early-stage detection rate* was downgraded to low GRADE because of study limitations (-1; risk of bias because of reference standard and flow and timing) and applicability (-1; bias due to indirectness because study population is not corresponding with population in the Netherlands).

Overall survival

The level of evidence regarding the outcome measure *overall survival* was to very low GRADE because applicability (-2; bias due to indirectness because study population and study design is not corresponding with the PICRO) and number of included patients (-1; imprecision because the confidence intervals including the possibility of a negative effect, no effect or a positive effect).

Costs

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 *costs* was downgraded to very low GRADE because of study limitations (-1; risk of bias because of describing of the study population, measuring and value of outcome measures) and applicability (-1; bias due to transferability to the surveillance setting in the Netherlands).

Conclusions based on the literature search

Sensitivity

Very low GRADE	The evidence is very uncertain about the *sensitivity* of MRI compared to ultrasound in patients under surveillance for HCC. *Sources: (Kim, 2016; Park, 2020; Park, 2021; Sutherland, 2017)*

Negative predictive value

Low GRADE	The evidence suggest that MRI may result higher *negative predictive value* than ultrasound in patients under surveillance for HCC. *Sources: (Kim, 2016; Park, 2020; Park, 2021; Sutherland, 2017)*

Specificity

Low GRADE	The evidence suggests that MRI may result higher *specificity* than ultrasound in patients under surveillance for HCC. *Sources: (Kim, 2016; Park, 2020; Park, 2021; Sutherland, 2017)*

Positive predictive value

Low GRADE	The evidence suggests that the *positive predictive value* of MRI is higher compared to ultrasound in patients under surveillance for HCC. *Sources: (Kim, 2016; Park, 2020; Park, 2021; Sutherland, 2017)*

(Very) early-stage detection rate

Low GRADE	The evidence suggests that MRI may result in higher *(very) early-stage detection rate* than ultrasound in patients under surveillance for HCC. *Sources: (Kim, 2016)*

Overall survival

Very low GRADE	The evidence is very uncertain about the effect on overall survival of surveillance by MRI compared to ultrasound. *Sources: (Kim, 2016)*

Recurrence-free survival

- GRADE	No evidence was found regarding the effect on recurrence-free survival of surveillance by MRI compared to surveillance by ultrasound

Costs

Very low GRADE	The evidence is very uncertain about the cost-effectiveness and the risk of harm of surveillance by MRI compared to ultrasound. *Sources: (Kim, 2019; Lima, 2019; Nahon, 2022; Tan, 2021)*

Overwegingen – van bewijs naar aanbeveling

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

De systematische zoekactie resulteerde in acht studies waarin zowel MRI als echografie voor surveillance bij dezelfde patiënten vergeleken werden. Het betrof vier diagnostische accuratesse studies (Kim, 2016; Park, 2020; Park, 2021; Sutherland, 2017) en vier kosten-effectiviteitsstudies (Kim, 2019; Lima, 2019; Nahon, 2022; Tan, 2021).

Voor de cruciale uitkomstmaten sensitiviteit en negatief voorspellende waarde voor detectie van HCC in een vroeg stadium, werden er door één studie uitkomsten gerapporteerd (Kim, 2016). In deze studie was de sensitiviteit voor detectie van HCC in een vroeg stadium voor MRI 0.86 en voor echografie 0.26. De negatief voorspellende waarde voor detectie van HCC in een vroeg stadium in deze studie voor MRI was 99% en voor echografie 97%.

Voor de uitkomstmaten sensitiviteit en negatief voorspellende waarde voor detectie van HCC ongeacht het stadium, werden door alle vier diagnostische accuratesse studies relevante uitkomsten gerapporteerd. De vier studies hebben naar verschillende modaliteiten van MRI (verkorte MRI, MRI zonder contrast, MRI volgens standaard protocol) gekeken en

voor alle modaliteiten werd een voordeel voor MRI gevonden ten opzichte van echografie. De sensitiviteit van echografie voor de studie van Kim (2016) is 0.28. De studies van Park (2020) en Park (2021) gebruiken andere MRI protocollen en data dan de oorspronkelijke studie van Kim (2016), maar dezelfde data voor echografie, vandaar dat de sensitiviteit van echografie in de studies van Park (2020) en Park (2021) ook op 0.28 ligt. De studie van Sutherland geeft een sensitiviteit van 1.00 voor echografie. Dit kan een overschatting zijn ten gevolge van kleine patiënten aantallen en beperkte duur van follow up).

De negatief voorspellende waarden voor HCC ongeacht het stadium van MRI liggen tussen de 99.0 en 99.4 procent. Voor echografie liggen deze tussen de 97 en 100 procent.

Voor de belangrijke uitkomstmaten specificiteit, positief voorspellende waarden en algehele overleving, werden ook uitkomsten gerapporteerd. Met betrekking tot de specificiteit voor detectie van HCC in een vroeg stadium heeft er één studie gegevens gerapporteerd (Kim, 2016). De specificiteit voor detectie van HCC in een vroeg stadium voor MRI was 0.97 en voor echografie 0.94. De positief voorspellende waarde voor detectie van HCC in een vroeg stadium in deze studie voor MRI was 53% en voor echografie 16%.

Vier studies rapporteerden de uitkomsten specificiteit en positief voorspellende waarde voor detectie van HCC ongeacht het stadium waarbij in alle vier studies een voordeel voor de MRI werd gezien.

Eén studie (Kim 2016) rapporteerde algehele overleving: de 3-jaars overleving was 86% voor patiënten in het surveillance programma die HCC ontwikkelden en 94% voor patiënten in het surveillance programma die geen HCC ontwikkelden gedurende follow up.

Voor de uitkomst ziektevrije overleving werden in geen van de geïncludeerde studies uitkomsten gerapporteerd.

De bewijskracht voor de diagnostische test accuratesse uitkomstmaten is laag. Dit heeft te maken met het risico op bias vanwege de flow en timing van de diagnostiek en referentie testen in de studies en het gebruik van verschillende referentie testen.

Er is één studie met lage aantallen geïncludeerde patiënten en beperkte follow up duur die een hoge sensitiviteit voor echografie veroorzaakt (Sutherland, 2017). De andere drie studies die naar verschillende vormen van MRI kijken, gebruiken wel hetzelfde echografisch onderzoek bij dezelfde patiënten (Kim, 2016; Park, 2020; Park, 2021). Ten slotte zijn de in onze search gevonden studies niet helemaal representatief voor de Nederlandse situatie, waar in de patiënten in een surveillance traject enerzijds veel minder vaak hepatitis B de onderliggende oorzaak van de leverziekte is en anderzijds veel vaker sprake is van cirrose (Van Meer, 2015).

Door de lage bewijskracht kunnen er op basis van onze literatuur search geen harde conclusies getrokken worden. Wel suggereren onze bevindingen dat dat MRI sensitiever en specifieker is, en een hogere negatief en positief voorspellende waarde zou kunnen hebben met een hogere detectie graad in een vroeg (nog curatief te behandelen) stadium.

Dit wordt ondersteund door verschillende meta-analyses waarin uitsluitend naar de waarde van MRI of uitsluitend naar de waarde van echografie gekeken is voor HCC surveillance. Een meta-analyse waarbij er wordt gekeken naar de diagnostische accuratesse van MRI, laat een sensitiviteit van 86 procent en een specificiteit van 94 procent zien voor een verkort (non-

contrast) MRI protocol (Gupta, 2021). Een meta-analyse waarbij er wordt gekeken naar de diagnostische accuratesse van echografie, laat een sensitiviteit van 78% zien voor detecteren van HCC ongeacht het stadium (door combinatie van echografie met AFP steeg de sensitiviteit tot 97%, ten koste van een lagere specificiteit) en een sensitiviteit van 45% zien voor het detecteren van HCC in een vroeg stadium (door combinatie van echografie met AFP steeg de sensitiviteit tot 63%, ten koste van een lagere specificiteit) (Tzartzeva, 2018). Volgens een andere recente meta-analyse was HCC surveillance met echo ± AFP bij patiënten met cirrose geassocieerd met frequentere detectie van HCC in een vroeg stadium, meer curatieve behandeling en een langere overleving (Singal, 2022). In deze meta-analyse worden ook 4 studies beschreven waarin gekeken is naar schade ('harm') ten gevolge van HCC surveillance. Schade ontstond bij 9-27% van de patiënten, in de meeste gevallen mild (bijvoorbeeld een aanvullende MRI of CT in verband met een fout-positieve echo) of matig (tumorbiopt in verband met een fout-positieve echo). Hoewel MRI surveillance waarschijnlijk minder schade door fout-positieve uitslagen zal veroorzaken dan echografie, zijn er geen gegevens hierover in de westerse setting. Ook zijn er geen data over het risico op andere vormen van door MRI veroorzaakte schade (met name in Westerse setting bij langdurige inclusie in een surveillance programma) en over de cost-benefit ratio.

Hoewel cirrose leidt een verhoogd risico op HCC, verschilt de jaarlijkse HCC incidentie aanzienlijk, afhankelijk van de onderliggende oorzaak van de cirrose. Als grens wordt vaak aangenomen een jaarlijkse HCC incidentie van 1,5% bij cirrose en van 0,2 tot 0,5% voor patiënten zonder cirrose (indien geen sprake is van cirrose zal de te verwachten winst van vroege HCC detectie groter zijn, omdat er meer curatieve mogelijkheden dan zijn bij cirrose). Er zijn verschillende subgroepen met cirrose maar een (soms veel) lagere jaarlijkse HCC incidentie dan 1,5%. In het algemeen zal de kans op fout-positieve uitslagen en de daarmee **geassocieerde kans** op schade toenemen bij lagere HCC incidentie (Curran, 2023). Tot de subgroepen van patiënten met cirrose met een jaarlijkse HCC incidentie <1,5% behoren: 1) Cirrose door vasculaire oorzaken (rechts decompensatie, agenesie van venae portae, Budd Chiari syndroom); 2) Biliaire atresie/status na Kasai operatie; 3) Alfa 1 antitrypsine deficiëntie: 4. ziekte van Wilson. Een belangrijke vraag is of met de tegenwoordig beschikbare effectieve antivirale therapie, HCC surveillance gecontinueerd moet worden bij patiënten met cirrose en een genezen hepatitis C of een adequaat behandelde hepatitis B (onderdrukt HBV DNA onder antivirale therapie). Bij cirrose en onbehandelde chronische hepatitis B en C ligt de jaarlijkse HCC incidentie ruim boven de cut-off van 1.5% per jaar, maar na succesvolle behandeling daalt die met ongeveer 70%. Er zijn echter geen betrouwbare methoden om subgroepen te onderscheiden waarbij het HCC risico zodanig gedaald is dat van surveillance kan worden afgezien.

Voor patiënten met B en C blijft het advies daarom vooralsnog om de HCC surveillance te continueren indien voor de antivirale therapie er aanwijzingen waren voor cirrose (op basis van een leverbiopt, fibroscan, echografie of andere radiologische beeldvorming (Isfordink, 2021; Papatheodoridis, 2015).

<u>Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)</u>

In het algemeen zal de kans op fout-positieve uitslagen bij HCC surveillance groter worden en ook de winst in detectie van HCC lager zijn bij lagere HCC incidentie. Bij de beslissing tot HCC surveillance moet meegewogen worden of patiënt in aanmerking zou komen voor behandeling als er door surveillance een HCC ontdekt zou worden. Patiënten hebben vaak een te positief beeld van HCC surveillance (van Meer, 2016). Goede voorlichting over de verwachte voor- en nadelen van surveillance is daarom belangrijk voordat er een gezamenlijk besluit wordt genomen ('Shared decision making'). Vanwege de toegenomen

kans op fout-positieve uitslagen moet bij lage a priori kans op HCC, een bij HCC diagnose op basis van radiologische beeldvorming, bevestiging middels tumorbiopt nadrukkelijk overwogen worden.

Kosten (middelenbeslag)
Kosteneffectiviteitsstudies laten zien dat MRI gepaard gaat met beperkte hogere kosten in vergelijking met echografie. Daarnaast laten de studies zien dat MRI meer kost per gewonnen levensjaar (Quality Adjusted Life Year). Een recente studie in Europese setting laat bij incidentie van 3% toenemende kosten van €15,477 per gewonnen levensjaar zien voor MRI ten opzichte van echografie.

Aanvaardbaarheid, haalbaarheid en implementatie
Continuering van bestaand beleid wordt geadviseerd. De werkgroep is van mening dat er geen bezwaren of voorwaarden zijn voor aanvaardbaarheid, haalbaarheid of implementatie van de aanbeveling.

Aanbevelingen

Aanbeveling-1

Rationale van de aanbeveling: weging van argumenten voor en tegen de diagnostische procedure
De kans op HCC detectie in vroeg stadium, met curative behandeling, is groter en de overleving beter, als HCC in het kader van surveillance ontdekt wordt. Er zitten echter ook nadelen aan surveillance. De cost-benefit ratio is ongunstiger bij lagere a priori kans op HCC. In geval van cirrose door vasculaire oorzaken (rechts decompensatie, agenesie v portae, Budd Chiari syndroom), cirrose ten gevolge van biliaire atresie/status na Kasai operatie, cirrose door alfa 1 antitrypsine deficiëntie en cirrose door de ziekte van Wilson is de jaarlijkse HCC incidentie laag. HCC surveillance moet niet verricht worden als er geen behandel mogelijkheden zouden zijn bij HCC detectie. Voor HCC surveillance bij patiënten met NASH wordt verwezen naar de NASH richtlijn.

Overweeg de patiënt met significant verhoogd risico op HCC in een surveillance programma op te nemen.

Daarbij spelen ook de mogelijkheid tot HCC therapie bij eventueel ontdekken van HCC en de a priori kans op HCC bij deze patiënt een rol.

Patiënten met een verhoogd risico op HCC zijn:

- Patiënten met levercirrose.
- Patiënten met hepatitis B zonder cirrose maar wel aanvullende risico verhogende factoren zoals familiaire HCC, Chinese man > 40 jaar, Chinese vrouw > 50 jaar, Sub-Sahara Afrikaan > 20 jaar.

Bespreek het volgende met de patiënt:

- deelname aan leverkankersurveillance is een keuze die zowel voor- als nadelen kent;
- als leverkanker bij surveillance ontdekt wordt, is er vaker sprake van nog curatief te behandelen stadium, met betere kansen op overleving.
- bij leverkanker surveillance worden tumoren vaak gemist. Een goede uitslag is dus geen garantie dat er geen afwijking is.

- ongeveer 1 tot 2 van de 10 mensen die deelnemen aan leverkankersurveillance zullen een keer “vals alarm” krijgen binnen drie jaar. Dit kan leiden tot stress, (achteraf) onnodige extra onderzoeken en een klein risico op complicaties.

Verricht geen surveillance bij patiënten waarbij een behandeling voor hepatocellulair carcinoom geen gunstige bijdrage heeft op de levensverwachting zoals bij patiënten in een slechte algemene conditie en/of met een beperkte levensverwachting.

Aanbeveling-2

Rationale van de aanbeveling: weging van argumenten voor en tegen de diagnostische procedure

Meta-analyses suggereren dat MRI sensitiever en specifieker is dan echografie voor de detectie van HCC, zowel curatief stadium als alle stadia: zowel standaard MRI als MRI met verkort protocol/zonder contrast). Er zijn echter weinig studies die MRI en echo bij dezelfde patiënt vergelijken (geen enkele in Westerse setting), en onvoldoende gegevens over risico’s van MRI (met name bij langdurige surveillance) en over kosten-baten analyse. Bij onvoldoende kwaliteit van echografische surveillance is surveillance middels MRI met of zonder alfa-foetoproteine de methode van voorkeur. Omdat echografie maar een beperkte sensitiviteit heeft voor detectie van HCC in een vroeg (curatief te behandelen) stadium, kan overwogen worden om ook AFP te bepalen. Hierdoor stijgt de sensitiviteit, ten koste van een lagere specificiteit. Fout positieve uitslagen komen vooral voor als de transaminasen verhoogd zijn. De US-Lirads klassificatie (Visualizatie A (geen of geringe limitatie), Visualizatie B (matige limitaties) en Visualisatie C (ernstige limitaties) geeft de mogelijkheid om tot een objectievere beschrijving en beoordeling van de kwaliteit van het echografisch onderzoek te komen (www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/Ultrasound-LI-RADS-v2017). Bij visualisatie kwaliteit C dient aanvullende beeldvorming middels MRI lever of 3 fasen CT-scan verricht te worden.

Verricht bij voorkeur echografie met beschrijving volgens US-LIRADS classificatie met of zonder alfa-foetoproteine elke 6 maanden voor surveillance op HCC bij patiënten met significant verhoogd risico op HCC.

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Bijlagen bij module 1

Kennislacunes

- Wel of niet AFP in combinatie met echografie
- Tweede goede studie (liefst in) Westerse setting naar waarde van MRI in vergelijking met echografie
- Screeningsinterval afhankelijk van screeningsmodaliteit? Wanneer er met MRI gescreend wordt, kan het interval dan verlengd worden? Ten aanzien van diagnostische accuratesse en daarnaast kosteneffectiviteit.

Zoekverantwoording

Algemene informatie

Richtlijn: NVMDL Hepatocellulair carcinoom	
Uitgangsvraag: Wat is de waarde van de MRI-scan voor surveillance bij patiënten met een verhoogd risico op hepatocellulair carcinoom?	
Database(s): Ovid/Medline, Embase	Datum: 27-1-2022
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. Voor deze vraag is gebruik gemaakt van de zoekblokken: MRI: https://blocks.bmi-online.nl/catalog/192 en Echografie: https://blocks.bmi-online.nl/catalog/349	
Toelichting: Voor deze vraag is gezocht met de volgende elementen: Hepatucellulair carcinoom EN MRI EN echografie EN sens, spec Omdat het aantal gevonden referenties aanzienlijk is en er naar de verdenking op hepatocellulair carcinoom wordt gezocht, is niet gezocht met liver disease of cirrhosis. Indien blijkt dat de juiste literatuur niet wordt gevonden, kunnen deze termen altijd nog worden toegevoegd. Vanwege de hoge aantallen is ook de keuze gemaakt om de comparison, **echografie**, mee te nemen. Om deze reden wordt het artikel van Xiong gemist. Het totaal aantal referenties in 1 database wordt dan 518. Het betekent dat er nog ca. 30% meer referenties in de tweede database gevonden zullen worden. Xiong J, Luo J, Bian J, Wu J. Overall diagnostic accuracy of different MR imaging sequences for detection of dysplastic nodules: a systematic review and meta-analysis. Eur. Radiol. 2021	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 9 februari 2022 met relevante zoektermen gezocht naar systematische reviews en RCTs over de waarde van de MRI-scan voor surveillance bij patiënten met een verhoogd risico op hepatocellulair carcinoom. De literatuurzoekactie leverde 493 unieke treffers op.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	34	26	45
RCTs			
Observationele studies	362	322	448
Overig			
Totaal			493

Zoekstrategie

Embase

No.	Query	Results
#22	#4 NOT #20 Artikel Xiong niet gevonden	**1**
#21	#4 AND #20	**2**
#20	#17 OR #18 OR #19	**371**
#19	(#13 OR #14) AND #16 Observationeel	**362**
#18	#12 AND #16	**15**
#17	#11 AND #16 SR	**34**
#16	#15 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)	**620**
#15	#9 AND #10	**1349**
#14	'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	**12836329**

No.	Query	Results
	(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 versus: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 versus: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)))	
#13	'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**
#12	'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**
#11	'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	**733409**

No.	Query	Results
	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	
#10	'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	**8425978**
#9	#7 AND #8	**4647**
#8	'echography'/exp OR 'color ultrasound flowmetry'/exp OR ultraso*:ab,ti OR sonograph*:ab,ti OR echograph*:ab,ti OR echotomograph*:ab,ti	**1242401**
#7	#5 AND #6	**15678**
#6	'nuclear magnetic resonance imaging'/exp/mj OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ab,ti OR fmris:ab,ti	**991570**
#5	'liver cell carcinoma'/exp/mj OR ('liver cancer'/de AND 'primary tumor'/de) OR (((hepat* OR liver) NEAR/3 carcinom*):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw OR ((primary NEAR/3 liver):ti,ab,kw)	**215358**
#4	#1 OR #2 OR #3	**3**

No.	Query	Results
#3	overall AND diagnostic AND accuracy AND different AND mr AND imaging AND sequences AND for AND detection AND of AND dysplastic AND nodules	1
#2	mri AND 'liver specific' AND contrast AND for AND surveillance AND patients AND with AND cirrhosis AND at AND high AND risk AND of AND hepatocellular AND carcinoma AND kim AND 2017 AND mri:ti	1
#1	abbreviated AND mri AND for AND hepatocellular AND carcinoma AND screening AND gupta AND 2021	1

Ovid/Medline

#	Searches	Results
14	9 and 12 Observationeel	322
13	6 and 12 SR	26
12	11 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	565
11	limit 10 to yr="2010 -Current"	575
10	4 and 5	938
9	7 or 8	6732831
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	5081424

	(confounding adj6 adjust*).ti,ab. or (versus or versus 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 versus 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.))	
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)	4066127
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/))	546658
5	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/	7251364
4	1 and 2 and 3	1785
3	exp Ultrasonography/ or ultraso*.ti,ab,kf. or sonograph*.ti,ab,kf. or echograph*.ti,ab,kf. or echotomograph*.ti,ab,kf.	697314

2	exp magnetic resonance imaging/ or ("magnetic resonance" and (image or images or imaging)).ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or "mr tomography".ti,ab,kf. or "mr tomographies".ti,ab,kf. or "mr tomographic".ti,ab,kf. or "proton spin".ti,ab,kf. or ((magneti* or "chemical shift") and imaging).ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf.	873800
1	Carcinoma, Hepatocellular/ or (hepat* adj3 carcinom*).ti,ab,kf. or hepatocarcinom*.ti,ab,kf. or hepatoma.ti,ab,kf. or (liver adj3 primary).ti,ab,kf.	160682

Evidencetabellen

Evidence table 1: Diagnostic test accuracy studies

Research question: What is de diagnostic value of the Magnetic Resonance Imaging (MRI) scan when compared with ultrasound (US) for patients with an indication for HCC surveillance and what is the incidence of detected HCC, percentage curative treated patients, overall and recurrence-free survival and the costs of MRI when compared with ultrasound?

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Kim, 2016	Type of study[1]: Prospective study Setting and country: Single academic tertiary care center, Korea Funding and conflicts of interest: Supported by Bayer Healthcare, which also provided the study drug (gadoxetic acid). Bayer was permitted to review the manuscript and	Inclusion criteria: - Age of 20 years or older - Presence of cirrhosis with estimated annual HCC risk of more than 5% (Risk of Hepatocellular carcinoma (HCC) was estimated by using a model, if risk index was greater than 2.33 that was estimated to correspond to an annual risk of	<u>Index test:</u> Liver Magnetic Resonance Imaging (MRI) with 1.5-T scanner (Magnetom Avanto; Siemens). Gadoxid acid (Primovist; Bayer) was administered at a dose of 0.025 mmol/kg. Axial T1-weighted images of the arterial, portal, delayed and hepatobiliary phases were obtained at 4-mm slice thickness.	<u>Reference test[2]:</u> Dynamic Computed Tomography (CT) scan and biopsy US guided or if a lesion was detected only by MRI, real-time US-CT fusion image guided. Cut-off point(s): Confirmation of HCC was based on results of histologic examination and/or typical CT images with nodule > 1 cm with arterial	Time between the index test en reference test: When MRI or US examination detected a nodule scored as category 5 or 4, a recall process with dynamic 4-phase CT scan was performed within three months. At 6-months after last screening round, all study patients were followed up with dynamic CT.	Outcome measures and effect size (include 95%CI and p-value if available): <u>Diagnostic accuracy MRI:</u> Detection rate for any HCC (sensitivity): 60.5% Detection rate for very-early and early-stage	*Authors conclusion:* Results of this study support our hypothesis that MRI with liver-specific contrast is more sensitive than US to detect early stage HCC in high-risk patients with cir-rhosis. For very early stage HCC (single lesion <2 cm), MRI screening yielded a detection rate of 84.8%, significantly higher than the

	suggest changes but had no role in study design, data collection, analysis, decision to publish or preparation of the manuscript	developing HCC of more than 5%) - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 - Absence of previous history of current suspicion of HCC Exclusion criteria: - Child-Pugh class C liver function - Estimated glomerular filtration rate < 30ml/min/1.73m^2 N=407 Prevalence: 10% Age in years, median (IQR): 56 (52-62) Sex: 56.5% Male / 43.5% Female Other important characteristics: Cause of cirrhosis, N (%): Hepatitis B virus: 288 (70.8%)	Three rounds of MRI screening every six months. Cut-off point(s): Positive screening criterion category 5 on a 5-point scale for MRI indicating the likelihood of HCC. <u>Comparator test:</u> Ultrasonographic (US) examinations. Three rounds of US screening every six months. Cut-off point(s): Positive screening criterion category 4 on a 4-point standardized scale for US indicating the likelihood of HCC.	hypervascularity and portal/delayed-phase washout as recommended by practice guidelines.	For how many participants were no complete outcome data available: N=49 o N=38: Logistic problems o N=10: Death o N=1: Other	HCC (sensitivity): 59.5% Detection rate very-early stage HCC (sensitivity): 54.5% Specificity: 99.3% False-negative rate: 39.5% False-positive rate: 0.7% Positive predictive value: 78.8% <u>Diagnostic accuracy US:</u> Detection rate for any HCC (sensitivity): 27.9% Detection rate of very early and early stage HCC (sensitivity): 26.2%	27.3% detected by US. Only 27.9% of the cancers were detected by US, which is far lower than reported in other meta-analyses. Possible explanation is that MRI was able to detect tumors far earlier in development than US. Model to estimate risk of HCC: Risk index=1.41 (if age > 50 years) + 1.65 (prothrombin activity <75%) + 0.92 (platelet count is <100x10^3/mm^3) + 0.74 (if anti hepatitis C virus antibody or hepatitis B virus surface antigen test is positive) Sponsor (Bayer) partially funded the study and review the manuscripts and suggest changes.

		Hepatitis C virus: 37 (9.1%) Alcohol: 52 (12.8%) Other: 30 (7.4%) Child-Pugh score class A, N (%): 320 (78.6%) Child-Pugh score class B, N (%): 87 (21.4%) Alpha-fetoprotein in mg/dl, median (IQR): 3 (2-5)				Detection rate very early stage HCC (sensitivity): 27.3% False negative rate: 72.1% Specificity: 94.4% False positive rate: 5.6% Positive predictive value: 16.9% <u>Incidence rate detected HCC:</u> N=43/407 (10.6%)	
Park, 2020	Type of study: Retrospective analysis of prospectively collected data[a] Setting and country: Single, academic, tertiary center, Korea Funding and conflicts of interest: Original study was funded by Bayer. For this retrospective analysis,	Inclusion criteria: - Age of 20 years or older - Presence of cirrhosis with estimated annual HCC risk of more than 5% (Risk of Hepatocellular carcinoma (HCC) was estimated by using a model, if risk index was greater than 2.33 that was	<u>Index test:</u> Liver Magnetic Resonance Imaging (MRI) with 1.5-T scanner (Magnetom Avanto; Siemens). The stimulated non-enhance MRI set consisted of axial DWI and T2WI. Three rounds of MRI screening every six months.	<u>Reference test:</u> Dynamic Computed Tomography (CT) scan, biopsy and/or subsequent surveillance round(s) after six months. Cut-off point(s): Confirmation of HCC was based on results of histologic examination and/or typical CT images with	Time between the index test and reference test: When MRI or US examination detected a nodule scored as category 5 or 4, a recall process with dynamic 4-phase CT scan was performed within three months. At 6-months after last screening round, all study patients were followed up with dynamic CT.	Outcome measures and effect size (include 95%CI and p-value if available): <u>Diagnostic accuracy non-enhanced MRI:</u> Per-lesion sensitivity: 77.1% (N=37/48)	*Authors conclusion:* This study demonstrated that non-enhanced MRI showed significantly better performance than US as a surveillance tool for HCC in a prospectively gathered cohort at a high risk of HCC.

	authors received no financial support and declare no conflicts of interest	estimated to correspond to an annual risk of developing HCC of more than 5%) - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 - Absence of previous history of current suspicion of HCC Exclusion criteria: - Child-Pugh class C liver function - Estimated glomerular filtration rate < 30ml/min/1.73m^2 - Withdrawn from study or died without subsequent follow-up examinations N=382 Prevalence: 5% Age in years, median (IQR): 56.4 (29-77)	Cut-off point(s): Lesion ≥ 1 cm. with either diffusion restriction or mild to moderate T2 hyperintensity. <u>Comparator test:</u> Ultrasonographic (US) examinations by 4-board certified abdominal radiologist using a convex probe (SC6-1, Supersonic Image SA; Aixplorer, France). Three rounds of US screening every six months. Cut-off point(s): Focal lesions ≥ 1 cm on US that met 1 or more of the following criteria, were considered positive: i) discrete focal mass distinguishable from the adjacent parenchyma, ii) peripheral low echoic halo, iii) mosaic pattern, and iv) definite tumor thrombi visible on US.	nodule > 1 cm with arterial hypervascularity and portal/delayed-phase washout as recommended by practice guidelines.	Average duration of follow-up after last surveillance: 32.9 months (range 1-60 months) For how many participants were no complete outcome data available: N=43 o N=34: Withdrawn from study o N=9: Death	(95%CI 63.2-86.8) Per-lesion positive predictive value: 56.9% (N=37/65) (95%CI 44.9-69.0) Per-exam sensitivity: 79.1% (N=34/43) (95%CI 64.4-88.7) Per-exam positive predictive value: 61.8% (N=34/55) (95%CI 49.0-74.7) Per-exam specificity: 97.9 (N=993/1014) (95%CI 96.8-98.7) <u>Diagnostic accuracy US:</u> Per-lesion sensitivity:	Model to estimate risk of HCC: Risk index=1.41 (if age > 50 years) + 1.65 (prothrombin activity <75%) + 0.92 (platelet count is <100x10^3/mm^3) + 0.74 (if anti hepatitis C virus antibody or hepatitis B virus surface antigen test is positive) Reference testing is CT, biopsy and/or subsequent surveillance round(s) after six months.

		Sex: 56.8% Male /43.2% Female Other important characteristics: Cause of cirrhosis, N (%): Hepatitis B virus: 276 (72.3%) Alcohol-induced: 46 (12.0%) Hepatitis C virus: 34 (8.9%) Other: 26 (6.8%) Alpha-fetoprotein in ng/ml, median (IQR): 7.0 (2.5-5.6)				25.0% (N=12/48) (95%CI 14.8-39.1) Per-lesion positive predictive value: 16.7% (N=12/72) (95%CI 8.1-25.3) Per-exam sensitivity: 27.9% (N=12/43) (16.6-43.0) Per-exam positive predictive value: 17.7% (N=12/68) (95%CI 8.6-26.7) Per-exam specificity: 94.5% (N=958/1014) (95%CI 92.9-95.7)	
Park, 2021	Type of study: Retrospective analysis of prospectively collected data[a]	Inclusion criteria: - Age of 20 years or older	<u>Index test:</u> The CAA approach consisted of first round using Magnetic Resonance	<u>Reference test:</u> Dynamic CT-scan, biopsy and/or	Time between the index test and reference test: Observations found on MRI or US fulfilling the positive	Outcome measures and effect size (include 95%CI	*Authors conclusion:* The performance of ultrasound, the current primary

	Setting and country: Single, academic, tertiary center, Korea Funding and conflicts of interest: Original study was funded by Bayer. For this retrospective analysis, dr. Amit Singal has served as a consultant for Bayer, Wako Diagnostics, Glycotest, Exact Science, Roche and TARGET pharmasolutions. Dr. Sang Hyun Choi received grants from Bayer outside the study. None of the authors declare conflicts of interest that pertain to this work	- Presence of cirrhosis with estimated annual HCC risk of more than 5% (Risk of Hepatocellular carcinoma (HCC) was estimated by using a model, if risk index was greater than 2.33 that was estimated to correspond to an annual risk of developing HCC of more than 5%) - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 - Absence of previous history of current suspicion of HCC Exclusion criteria: - History of suspicion of any type of malignancy, significant comorbidities with a predicted survival period < 3 years - Estimated Glomerular Filtration	Imaging (MRI) with 1.5-T scanner (Magnetom Avanto; Siemens). and included T1-weighted imaging, DWI, T2WI and contrast-enhanced T1-weighted imaging and the second and third round using Abbreviated MRI (AMRI) which consisted of DWI, T2WI and HBP imaging Cut-off point(s): LI-RADS, CMRI-3 which included LR-4, LR-5, LR-TIV and LR-M <u>Index test 2:</u> The AAA approach consisted of three rounds using AMRI Cut-off point(s): LI-RADS, AMRI-3 which included observation(s) ≥ 10 mm that were not definitely benign, changes in imaging characteristics or threshold growth of previously noted	Cut-off point(s): Observations showing features of definite HCC on dynamic CT (nodules > 10 mm with arterial hyperenhancement and washout).	screening criteria underwent a recall process with dynamic CT scan performed within 3 months. Observations that were not diagnostic on CT underwent pathologic confirmations. After the third round all patients underwent dynamic CT at six months. Identity of false positive observations was determined by thoroughly review all available follow-up imaging and pathology data. Median follow-up after last round of surveillance: 40.6 months (IQR 17.5-51.3) For how many participants were no complete outcome data available: N=20 ○ N=13: Withdrawn from study ○ N=5: Death ○ N=2: Incomplete MRI	and p-value if available): <u>Diagnostic accuracy CAA approach:</u> Per-examination sensitivity round 1: 96.4% (N=27/28) (95%CI 78.6-99.5) Per-examination sensitivity round 2-3: 80% (N=12/15) (95%CI 53.0-93.4) Per-examination sensitivity total: 90.7% (N=39/43) (95%CI 77.7-96.5) Per-examination specificity round 1: 96.9% (N=343/354) (95%CI 94.5-98.3)	surveillance modality for HCC, is suboptimal in detecting early-stage HCC. We found that in a prospective cohort of high-risk patients, AMRI-based approaches had significantly higher sensitivity for detecting early- stage HCC than an ultrasound-only approach. Model to estimate risk of HCC: Risk index=1.41 (if age > 50 years) + 1.65 (prothrombin activity <75%) + 0.92 (platelet count is $<100x10^3/mm^3$) + 0.74 (if anti hepatitis C virus antibody or hepatitis B virus surface antigen test is positive) If a patient had any lesion(s) fulfilling the positive criteria of the simulated surveil-lance test without confirmatory CT or histologic results and

		Rate (GFR) < 30 ml/min/1.73m^2 - Child Pugh class C - Contra indications for MRI N=382 Prevalence: 5% Age in years, median (IQR): 56 (29-77) Sex: 56.8% Male /43.2% Female Other important characteristics: Cause of cirrhosis, N (%): Hepatitis B virus: 276 (72.3%) Alcohol-induced: 46 (12.0%) Hepatitis C virus: 34 (8.9%) Other: 26 (6.8%) Alpha-fetoprotein in ng/ml, median (IQR): 7.0 (2.5-5.6)	observation(s) and new thrombus in vein. <u>Comparator test:</u> Ultrasound approach consisting of three rounds of ultrasound. Cut-off point(s): US LI-RADS with US-3 including observations $\geq$ 10 mm that were not definitely benign, new thrombus in vein and threshold growth			Per-examination specificity round 2-3: 97.3% (N=640/658) (95%CI 95.6-98.3) Per-examination specificity total: 97.1% (N=983/1012) (95%CI 95.8-98.0) Per-examination accuracy round 1: 96.9% (N=343/382) (95%CI 94.6-98.2) Per-examination accuracy round 2-3: 96.9% (N=652/673) (95%CI 95.2-98.0) Per-examination accuracy total:	proceeded to the subsequent surveillance round, we used the CMRI of the subsequent round as a reference test for the previous observations. In this way, all simulated surveillance tests of each round had an available reference standard test (histology, dynamic CT, and/or subsequent surveillance CMRI within 6 months)

						96.9% (N=1022/1055) (95%CI 95.5-97.8) <u>Diagnostic accuracy AAA approach:</u> Per-examination sensitivity round 1: 89.3% (N=25/28) (95%CI 71.6-96.5) Per-examination sensitivity round 2-3: 80.0% (N=12/15) (95%CI 53.0-93.4) Per-examination sensitivity total: 86.0% (N=37/43) (95%CI 72.2-93.6) Per-examination specificity round 1: 92.4%	

						(N=327/354) (95%CI 89.1-94.7) Per-examination specificity round 2-3: 97.3% (N=640/658) (95%CI 95.6-98.3) Per-examination specificity total: 95.6% (N=967/1012) (95%CI 94.0-96.7) Per-examination accuracy round 1: 92.1% (N=352/382) (95%CI 89.0-94.5) Per-examination accuracy round 2-3: 96.9% (N=652/673) (95%CI 95.2-98.0)	

						Per-examination accuracy total: 95.2% (N=1004/1055) (95%CI 93.6-96.4) <u>Diagnostic accuracy US:</u> Per-examination sensitivity round 1: 39.3% (N=11/28) (95%CI 23.3-58.0) Per-examination sensitivity round 2-3: 6.7% (N=1/15) (95%CI 0.9-35.2) Per-examination sensitivity total: 27.9% (N=12/43) (95%CI 16.6-43.0) Per-examination specificity	

						round 1: 93.8% (N=332/354) (95%CI 90.7-95.9) Per-examination specificity round 2-3: 97.7% (N=643/658) (95%CI 96.3-98.6) Per-examination specificity total: 96.3% (N=975/1012) (95%CI 95.0-97.4) Per-examination accuracy round 1: 89.8% (N=343/382) (95%CI 86.3-92.5) Per-examination accuracy round 2-3: 95.7% (N=644/673) (95%CI 93.9-97.0)	

						Per-examination accuracy total: 93.5=6% (N=987/1055) (95%CI 91.8-94.9)	
Sutherland, 2017	Type of study: Prospective cohort study Setting and country: University-affiliated tertiary hospital, Australia Funding and conflicts of interest: The authors received no funding for this research and no authors have conflicts of interest to declare	Inclusion criteria: - Patients with age ≥ 18 years - Referred by the gastroenterology department with chronic liver disease for hepatocellular carcinoma screening liver ultrasound Exclusion criteria: - Presence of a known mass as indicated on the ultrasound request form - Non-English speaking - Contraindications to MRI such as pacemaker or contraindicated metallic implant N=192 Prevalence: 3% (N=6)	<u>Index test:</u> MRI scan sequence comprised respiratory-gated DWI with the following parameters: TR 2500; TE 80; slice thickness 8 mm; distance factor 30%; FOV read 400 mm with effective voxel size of 2.6 x 2.1 x 8 mm; and b values of 100, 400, 800 acquired with 8 averages Cut-off point(s): MRI lesions were considered suspicious if they had elevated signal on high b value DWI and were iso or hypointense to background liver on the ADC map <u>Comparator test:</u> Ultrasound	Describe reference test: Arterial phase hyperenhancement followed by washout on either CT or MRI or by histology (biopsy or resection) Cut-off point(s): AASLD guidelines	Time between the index test and reference test: Any suspicious lesion was documented with respect to size, features and hepatic segment. Prior imaging was reviewed to determine the aetiology of the lesion and assess stability. If lesion was new it sparked further investigation as per the AASLR guidelines, being repeat imaging in three months by the modality that identified it for lesions under 10 mm and cross-sectional contrast-enhanced multiphase imaging with MRI or CT for new lesions over 10 mm For how many participants were no complete outcome data available: N=31 (16%) Compliance rates for:	Outcome measures and effect size (include 95%CI and p-value if available): <u>Diagnostic accuracy MRI:</u> Sensitivity: 83% (N=5/6) Specificity: 98% Positive predictive value: 63% Negative predictive value: 99% <u>Diagnostic accuracy US:</u> Sensitivity: 100% (N=6/6) Specificity: 90%	

		Age in years, median (IQR): 58 (22-80) Sex: 72% Male / 28% Female Other important characteristics: Cause of chronic liver disease: Hepatitis B virus: N=108 (56%) Hepatitis C virus: N=56 (29%) Alcohol: N=21 (11%) Hepatic steatosis: N=8 (4%) Other: N=8 (4%)	Cut-off point(s): Lesions were suspicious if they were solid and not clearly focal fat infiltration or focal fat sparing.		○ Two examination rounds: N=91 (47%) ○ Three examination rounds: N=45 (23%) ○ Four examination rounds: N=23 (12%) ○ Five examination rounds: N=6 (3%) No reasons for incomplete outcome data described	Positive predictive value: 23% Negative predictive value: 100%	
[a] Data from study of Kim (2016)							

Evidence table 2: Cost-effectiveness studies

Research question: What is de diagnostic value of the MRI-scan when compared with ultrasound for patients with an indication for HCC surveillance and what is the incidence of detected HCC, percentage curative treated patients, overall and recurrence-free survival and the costs of MRI when compared with ultrasound?

Study reference	Study characteristics	Population[2]	Interventions	Outcome measures and effect size [4]	Incremental Costs/Effects	Comments
Kim, 2019	Study design (Trial/Model): Cohort-based Markov model Country: Korea Setting: Surveillance Perspective: Healthcare	Inclusion criteria: - Patients with compensated cirrhosis (Child-Pugh A) Exclusion criteria: Not specified	Describe interventions and comparators (treatments/procedures/tests): MRI and ultrasound were performed concurrently	*Outcome measures and effect size* *Annual HCC incidence 3% (base-case):* MRI: 11.101 Life Years US: 10.717 Life Years	ICER: Annual HCC Incidence 1%: 101,586 $/QALY Annual HCC Incidence 2%: 44,026 $/QALY	*Authors conclusion:* The present study demonstrated that MRI surveillance for HCC can be cost-effective in high-risk patients with compensated cirrhosis. Since MRI and ultrasound were performed concurrently and one HCC had been diagnosed with MRI, US detection was no longer an

	Time horizon: 20 years Price year (currency): 2018 Discounting: Costs: 5% per year Outcomes: 5% per year Source of funding: Supported by grants from Korean National Health Clinical Research project of the Ministry of Health and Welfare, the Korean Health Technology R&D Project, Ministry of Health and Welfare, the National Research Foundation of Korea, the Korean Gastroenterology Fund for Future Development, the National Evidence-Based Healthcare Collaborating Agency and the Technology Innovation Program funded by the Ministry of Trade, Industry, and Energy of the Republic of Korea.	<u>N total at baseline</u>: Interventions: 10,000 <u>Important prognostic factors</u>[2]: *Age: 50 years* *Surveillance cycle length: 6 months* *Number of health states included in the model: 11* *HCC incidence: 3%* *HCC stage at time of detection – very early stage:* *MRI: 72.1%* *US: 18.5%* *HCC stage at time of detection – very early + early stage:* *MRI: 97.7%* *US: 61.8%*		*Outcome measure and Costs Annual HCC incidence 3% (base-case):* MRI: 62,287 $ US: 56,725 $ *Cost-effectiveness outcome measures Annual HCC incidence 3% (base-case):* MRI: 6.783 QALYs US: 6.562 QALYs	Annual HCC Incidence 3%: 25,202 $/QALY Annual HCC Incidence 3.5%: 20,000 $/QALY Annual HCC Incidence 4%: 16,039 $/QALY Annual HCC Incidence 5%: 10,721 $/QALY	opportunity. Therefore detection rate data from US were extracted from another resource. Higher incidence of HCC, more patients developed HCC and further surveillance was not required, which had a considerable effect on the costs of surveillance.

		Sensitivity MRI: 85.7% *Sensitivity US (95%CI): 47.0% (33-61)*				
Lima, 2019	Study design (Trial/Model): decisional Markov model Country: Canada Setting: Surveillance Perspective: Healthcare Time horizon: Lifetime Price year (currency): 2017 Discounting: Costs: 1.5% per year Outcomes: 1.5% per year Source of funding: Supported by a New Researcher Startup Grant from the Centre de recherche du Centre hospitalier de l'Université de Montréal.	Inclusion criteria: - Patients with compensated cirrhosis (Child-Pugh A) - Age 50 years Exclusion criteria: Not specified N total at baseline: Interventions: Not specified Important prognostic factors[2]: *Age: 50 years* *Surveillance cycle length: 6 months* *Number of health states included in the model: Not specified*	Describe interventions and comparators (treatments/procedures/tests): Seven surveillance and diagnostic strategies were investigated with combinations of four imagine techniques (US, CT, complete MRI, abbreviated MRI). A) Surveillance US; diagnosis CT F) Surveillance MRI; if inadequate CT; diagnosis MRI Strategies were evaluated for: - Optimal scenario: 100% of the patients with compensated cirrhosis (Child-Pugh A) and an assumed compliance rate of 100%. - Conservative scenario: 29% of the patients with compensated cirrhosis (Child-Pugh A) and an assumed compliance rate of 52%.	*Cost-effectiveness outcome measures:* Optimal scenario (100% Child-Pugh A; 100% surveillance compliance) US: 7.269 QALY MRI: 7.424 QALY Conservative scenario (29% Child-Pugh A; 52% surveillance compliance) US: 4.300 QALY MRI: 4.354 QALY	*Incremental Effects:* Optimal scenario: 0.011 QALY Conservative scenario: 0.022 QALY *Incremental Costs:* Optimal scenario: 7293 Canadian dollars Conservative scenario: 873 Canadian dollars *ICER:* Optimal scenario: 663,000 Canadian dollars/QALY Conservative scenario: 39,681 Canadian dollars/QALY	*Authors conclusion:* In conclusion, in a scenario that assumes optimal patient compliance and takes into account inconclusive imaging examinations, CT for HCC surveillance and diagnosis and complete MRI for inadequate CT was most cost-effective

		HCC incidence: 3% *Sensitivity MRI (range): 86% (82-93)* *Sensitivity US (range): 78% (60-89)* *Specificity MRI (range): 86% (79-91)* *Specificity US (range): 89% (80-94)*				
Nahon, 2022	Study design (Trial/Model): Markov model with data from one RCT and three prospective cohort studies: CHC2000 trial, ANRS Co12 CirVir cohort, CIRRAL cohor and ANRS CO22 Hepather cohort Country: France Setting: Surveillance Perspective: Healthcare Time horizon: 20 years Price year (currency): 2020 Discounting: Costs: 2.5% per year Outcomes: 2.5% per year	<u>Inclusion criteria</u>: - Patients with biopsy proven compensated cirrhosis (Child-Pugh A) - Age 50 years <u>Exclusion criteria</u>: Not specified <u>N total at baseline</u>: Interventions: 10,000 <u>Important prognostic factors</u>[2]:	Describe interventions and comparators (treatments/procedures/tests): MRI versus Ultrasound	*Outcome measures and effect size:* MRI: 13.8 discounted life years US: 13.4 discounted life years *Outcome measure and Costs:* MRI: € 106,873 US: € 100,739	*ICER:* Incidence rate 3% per year: € 15,477/Life Year Incidence rate 2% per year: € 23,338/Life Year Gained Incidence rate 1% per year: € 47,194/Life Year Gained	*Authors conclusion:* Our prospective cohort- and model-based evaluation of very early HCC detection found that MRI monitoring was cost- effective for a baseline yearly incidence of 3% and over a range of assumptions on incidence, costs and treatment choice.

	Source of funding: The cohorts were funded by the French ministry of health, French Ligue de Recherche contre le cancer, National Agency for Research on HIV and Hepatitis, the French national institute of Cancer and the French association for Research in Cancer	*Age: 50 years* *Surveillance cycle length: 3 months* *Number of health states included in the model: 14* *HCC incidence: 3%* *Sensitivity MRI: 85.7%[a]*				
Tan, 2021	Study design (Trial/Model): Markov model Country: Singapore Setting: Surveillance Perspective: Healthcare Time horizon: 40 years Price year (currency): Not reported Discounting: Costs: 3% per year Effects: 3% per year Source of funding: Not reported	Inclusion criteria: - At risk patients Exclusion criteria: Not reported N total at baseline: Interventions: 482,000 Important prognostic factors[2]: *Average age: 40 years*	Describe interventions and comparators (treatments/procedures/tests): No surveillance versus Ultrasound surveillance versus Non-contrast Enhanced MRI (NCEMRI) surveillance	*Outcome measure and Costs, mean (SE):* No surveillance: 4,675 $ (263) US surveillance: 23,803 $ (367) NCEMRI surveillance: 177,876 $ (1111) *Cost-effectiveness outcome measures, mean (SE):* No surveillance: 7.483 QALY (0.044)	Incremental Effects: US surveillance: 3.759 QALY NCEMRI surveillance: 3.943 QALY NCEMRI versus US: 0.184 QALY Incremental Costs: US surveillance: 19,128 $ NCEMRI surveillance: 173,201 $ NCEMRI versus US: 154,073 $ *ICER:*	*Authors conclusion:* Despite NCEMRI having a superior diagnostic accuracy, it is a less cost- effective strategy than US for HCC surveillance in the general at-risk population, from an overall healthcare perspective. Future local cost-effectiveness analyses should include stratifying surveillance methods with a variety of imaging techniques (US, NCEMRI, CEMRI) based on patients' risk profiles. Relatively low transition probability of 1.1 percent compared with other studies, results in decreased cost-effectiveness.

		Surveillance cycle length: 6 months *Number of health states included in the model: 7* *HCC incidence: 1.1%* *Sensitivity MRI: 90%* *Sensitivity US: 55.6%* *Specificity MRI: 91.5%* *Specificity US: 93%*		US surveillance: 11.242 QALY (0.074) NCEMRI surveillance: 11.426 QALY (0.074)	US surveillance: 5,088$/QALY NCEMRI surveillance: 43,924$/QALY NCEMRI versus US: 837,353$/QALY	
[a] Data from the PRIUS study						

Risk of bias assessment table 1: diagnostic accuracy studies (QUADAS II, 2011)

Research question: What is de diagnostic value of the Magnetic Resonance Imaging (MRI) scan when compared with ultrasound (US) for patients with an indication for HCC surveillance and what is the incidence of detected HCC, percentage curative treated patients, overall and recurrence-free survival and the costs of MRI when compared with ultrasound?

5

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Kim, 2016	Was a consecutive or random sample of patients enrolled? Yes, consecutive sample of patients at risk for HCC Was a case-control design avoided? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? Yes, US and MRI interpretations were allocated to different radiologists who were blinded	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without	Was there an appropriate interval between index test(s) and reference standard? Yes, 3 months when positive screening criterion for MRI or US. 6 months for all study patients after last screening round.	Are there concerns that the included patients do not match the review question? Yes, high percentage of hepatitis B patients in the sample.

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
	Did the study avoid inappropriate exclusions? Yes, clear in- and exclusion criteria were reported	to the findings of the other imaging modalities. If a threshold was used, was it pre-specified? Yes, positive screening criterion category 5 or 4 on MRI or US (standardized 5-point scale for MRI or 4-point scale for US)	knowledge of the results of the index test? Unclear, it is not clear of the assessors of the reference standards (CT and biopsy) were blinded for results of the index or comparator tests.	Did all patients receive a reference standard? Yes, CT or CT and biopsy Did patients receive the same reference standard? Yes, patients received reference standard according to the AASLD criteria. Were all patients included in the analysis? Yes	Are there concerns that the index test, its conduct, or interpretation differ from the review question? No, MRI in the Netherlands is also gadoxetic enhanced. 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: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: UNCLEAR**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Park, 2020	Was a consecutive or random sample of patients enrolled? Yes, consecutive sample of patients at risk for HCC from study data of Kim (2016) Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes, clear in- and exclusion criteria were reported	Were the index test results interpreted without knowledge of the results of the reference standard? Yes, MRIs were anonymized, shuffled in random order an analysed by two reviewers who were blinded to data, pathological results, final diagnosis and results of full contrast-enhance MRI If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition? Yes, there were different reference standards: Dynamic CT, biopsy and and/or subsequent surveillance round(s) after six months. Were the reference standard results interpreted without knowledge of the results of the index test? Yes, results of reference standard tests were reviews by	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? Yes, patients received reference standard according to the AASLD criteria.	Are there concerns that the included patients do not match the review question? Yes, high percentage of hepatitis B patients in this sample 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

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
		Yes, lesions of ≥ 1 cm. with either diffusion restriction or mild to moderate T2 hyperintensity	one of the authors who was not involved in imaging analysis	Were all patients included in the analysis? Yes	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: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	
Park, 2021	Was a consecutive or random sample of patients enrolled? Yes, consecutive sample of patients at risk for HCC from study data of Kim (2016) 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? Yes, readers independently interpreted the MRIs in a blinded-to-outcome manner but were allowed to view MRI images of previous round(s) when they interpreted the second and third round MRI If a threshold was used, was it pre-specified? Yes, LI-RADS classifications was used	Is the reference standard likely to correctly classify the target condition? Unclear, CT and/or pathological confirmation and/or follow-up of medical records 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? Yes, patients received reference standard according to the AASLD criteria. Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? Yes, high percentage of hepatitis B patients in this sample 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: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: UNCLEAR**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Sutherland, 2017	Was a consecutive or random sample of patients enrolled? Yes, consecutive sample of patients referred by gastroenterology department with chronic liver disease 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? Yes, MRI was reviewed by radiologist blinded to the US and all prior imaging If a threshold was used, was it pre-specified? Yes	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	Was there an appropriate interval between index test(s) and reference standard? Yes, prior imaging was reviewed to determine aetiology and assess stability. If a lesion was new, further investigation as defined by the AASLR Did all patients receive a reference standard? Unclear, gold standard is reported but not if all patients received reference standard Did patients receive the same reference standard? Unclear, gold standard is arterial phase hyperenhancement follow by washout on CT or MRI or histology Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? Unclear, study population are patients with chronic liver diseases 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: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: UNCLEAR**	CONCLUSION Could the patient flow have introduced bias? **RISK: UNCLEAR**	

Risk of Bias assessment table 2: Cost-effectiveness studies: CHEC-list

Research question: What is de diagnostic value of the Magnetic Resonance Imaging (MRI) scan when compared with ultrasound (US) for patients with an indication for HCC surveillance and what is the incidence of detected HCC, percentage curative treated patients, overall and recurrence-free survival and the costs of MRI when compared with ultrasound?

Study reference (first author, publication year)	**1 Y/N**	**2 Y/N**	**3 Y/N**	**4 Y/N**	**5 Y/N**	**6 Y/N**	**7 Y/N**	**8 Y/N**	**9 Y/N**	**10 Y/N**	**11 Y/N**	**12 Y/N**	**13 Y/N**	**14 Y/N**	**15 Y/N**	**16 Y/N**	**17 Y/N**	**18 Y/N**	**19 Y/N**	**20 Y/N**	**Comments**
Kim, 2019	Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NR	MRI and US were performed concurrently, one HCC had been diagnosed with MRI, US detection was no longer an opportunity. Therefore detection rate data from US was extracted from another resource.
Lima, 2019	Y		Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	NR	NR	Disutility associated with false-positive diagnosis was based on cost-effectiveness study of patients undergoing evaluation for coronary artery disease (overestimation of cost-effectiveness)
Nahon, 2022	Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Tan, 2021	N		Y	Y	Y	Y	Y	Y	Y	NR	N	NR	Y	Y	Y	N	Y	Y	NR	NR	Death as outcome is taken into account as all-cause death

Item	
1.	Is the study population clearly described?
2.	Are competing alternatives clearly described?
3.	Is a well-defined research question posed in answerable form?
4.	Is the economic study design appropriate to the stated objective?
5.	Are the structural assumptions and the validation methods of the model properly reported? (*only if model based*)
6.	Is the chosen time horizon appropriate to include relevant costs and consequences?
7.	Is the actual perspective chosen appropriate?
8.	Are all important and relevant costs for each alternative identified?
9.	Are all costs measured appropriately in physical units?
10.	Are costs valued appropriately?
11.	Are all important and relevant outcomes for each alternative identified?
12.	Are all outcomes measured appropriately?
13.	Are outcomes valued appropriately?
14.	Is an incremental analysis of costs and outcomes of alternatives performed?
15.	Are all future costs and outcomes discounted appropriately?
16.	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?
17.	Do the conclusions follow from the data reported?
18.	Does the study discuss the generalizability of the results to other settings and patient/ client groups?
19.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?
20.	Are ethical and distributional issues discussed appropriately?

Table of excluded studies

Reference	Reason for exclusion
Ahmed, N.N.A., El Gaafary, S.M., Elia, R.Z. *et al.* Role of abbreviated MRI protocol for screening of HCC in HCV related cirrhotic patients prior to direct-acting antiviral treatment. *Egypt J Radiol Nucl Med* **51**, 102 (2020). https://doi.org/10.1186/s43055-020-00199-x	Wrong setting: No surveillance setting
Chen VL, Singal AG, Tapper EB, Parikh ND. Hepatocellular carcinoma surveillance, early detection and survival in a privately insured US cohort. Liver Int. 2020 Apr;40(4):947-955. doi: 10.1111/liv.14379. Epub 2020 Jan 26. PMID: 31943689; PMCID: PMC8047296.	Indirect evidence: No direct comparison between index test and comparator test
Chou R, Cuevas C, Fu R, Devine B, Wasson N, Ginsburg A, Zakher B, Pappas M, Graham E, Sullivan SD. Imaging Techniques for the Diagnosis of Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. Ann Intern Med. 2015 May 19;162(10):697-711. doi: 10.7326/M14-2509. Erratum in: Ann Intern Med. 2015 Jun 16;162(12):880. PMID: 25984845.	Wrong setting: No surveillance setting
Colli A, Nadarevic T, Miletic D, Giljaca V, Fraquelli M, Štimac D, Casazza G. Abdominal ultrasound and alpha-foetoprotein for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease. Cochrane Database Syst Rev. 2021 Apr 15;4(4):CD013346. doi: 10.1002/14651858.CD013346.pub2. PMID: 33855699; PMCID: PMC8078581.	Indirect evidence: No direct comparison between index test and comparator test
Demirtas CO, Gunduz F, Tuney D, Baltacioglu F, Kani HT, Bugdayci O, Alahdab YO, Ozdogan OC. Annual contrast-enhanced magnetic resonance imaging is highly effective in the surveillance of hepatocellular carcinoma among cirrhotic patients. Eur J Gastroenterol Hepatol. 2020 Apr;32(4):517-523. doi: 10.1097/MEG.0000000000001528. PMID: 31524775.	Indirect evidence: No direct comparison between index test and comparator test
Gupta P, Soundararajan R, Patel A, Kumar-M P, Sharma V, Kalra N. Abbreviated MRI for hepatocellular carcinoma screening: A systematic review and meta-analysis. J Hepatol. 2021 Jul;75(1):108-119. doi: 10.1016/j.jhep.2021.01.041. Epub 2021 Feb 3. PMID: 33548385.	Indirect evidence: No direct comparison between index test and comparator test

Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, Waljee AK, Singal AG. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 2018 May;154(6):1706-1718.e1. doi: 10.1053/j.gastro.2018.01.064. Epub 2018 Feb 6. PMID: 29425931; PMCID: PMC5927818.	Indirect evidence: No direct comparison between index test and comparator test
Vietti Violi N, Lewis S, Liao J, Hulkower M, Hernandez-Meza G, Smith K, Babb JS, Chin X, Song J, Said D, Kihira S, Sirlin CB, Reeder SB, Bashir MR, Fowler KJ, Ferket BS, Sigel K, Taouli B. Gadoxetate-enhanced abbreviated MRI is highly accurate for hepatocellular carcinoma screening. Eur Radiol. 2020 Nov;30(11):6003-6013. doi: 10.1007/s00330-020-07014-1. Epub 2020 Jun 25. PMID: 32588209.	Indirect evidence: No direct comparison between index test and comparator test
Yu NC, Chaudhari V, Raman SS, Lassman C, Tong MJ, Busuttil RW, Lu DS. CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. Clin Gastroenterol Hepatol. 2011 Feb;9(2):161-7. doi: 10.1016/j.cgh.2010.09.017. Epub 2010 Oct 1. PMID: 20920597.	Wrong population: Population of pretransplant patiënts
Taylor EJ, Jones RL, Guthrie JA, Rowe IA. Modeling the benefits and harms of surveillance for hepatocellular carcinoma: Information to support informed choices. Hepatology. 2017 Nov;66(5):1546-1555. doi: 10.1002/hep.29315. Epub 2017 Oct 11. PMID: 28605060.	Indirect evidence: No direct comparison between index test and comparator test

Module 2 CT versus MRI

Uitgangsvraag

Welke modaliteit en scanprotocol zijn aangewezen voor diagnose van HCC?

Inleiding

Wanneer er een verdenking op HCC bij een patiënt is wordt er een 4-fasen CT-scan of contrast MRI uitgevoerd om een hepatocellulair carcinoom te detecteren. Zowel CT-scans als MR-beelden zijn zeer goed om de diagnose van een maligne focale leverlaesie te bevestigen. Meestal wordt er eerst een CT uitgevoerd en nadien beeldvorming met MR indien nodig. Een CT-scan is gemakkelijk en overal zeer snel toegankelijk. MR Imaging is uitstekend voor differentiatie, zeker bij problemen.

Search and select

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

What is the diagnostic accuracy of a CT-scan (using a scan protocol) compared to MR imaging (using a scan protocol) in patients with a focal liver lesion suspected of a hepatocellular carcinoma?

P: patients with a focal liver lesion suspected of a hepatocellular carcinoma;
I: CT-scan (using a scan protocol);
C: MR imaging (using a scan protocol);
R: CT or MRI for patients with cirrhosis; histology on biopsy or resected tissue for patients without cirrhosis; or a clinical follow-up of at least 6 months;
O: sensitivity, specificity, positive predictive value, negative predictive value, area under the curve, costs.

<u>Relevant outcome measures</u>

The guideline development group considered the specificity and positive predictive value as a critical outcome measure for decision making; and the sensitivity, negative predictive value, area under the curve, and costs 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.

<u>Search and select (Methods)</u>

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 23-06-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search filtered on systematic reviews resulted in 113 hits. Studies were selected based on the following criteria: all patients in the sample were suspected of a hepatocellular carcinoma, CT-scan was compared head-to-head to MR imaging, the reference standards were 1) histology on biopsies or resected tissue, or 2) CT or MRI findings (in patients with cirrhosis), or 3) a clinical follow-up of at least six months, at least one of the outcomes of interest was reported, the study was a systematic review, it was (at least) deducible which studies were included for a direct head-to-head comparison of CT and MRI. Forty-four studies were initially selected based on title and abstract screening. After reading the full text, 41 studies were excluded (see the table with reasons for exclusion under the tab Methods), and three systematic reviews were included.

Results

Three systematic reviews 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

Chen (2022) performed a systematic review and meta-analyses comparing contrast-enhanced CT-scans with extracellular contrast-enhanced MR imaging for diagnosing hepatocellular carcinomas in patients with chronic liver diseases. Studies were searched in Medline (through PubMed), Embase, Web of Science, and the Cochrane Library up to 1/5/'21. Studies were selected when the diagnostic performance of contrast-enhanced CT and of extracellular contrast-enhanced MRI were investigated in an adult population with chronic liver diseases for detecting hepatocellular carcinomas. Furthermore, the studied had to use pathologic evidence or and imaging follow-up (at least 6 months) as a reference standard, the studies could be retrieved, and the study reported head-to-head data sufficiently to construct 2-by-2 tables. Studies were excluded when the diagnostic accuracy of both modalities was not assessed or when no head-to-head comparison was available, were conference abstracts, case reports, commentaries, letters, reviews, meta-analyses, or other types of work. Ten primary studies were included and used for meta-analyses, of which 3 were retrospective and 7 were prospective. Number of patients in the samples ranged from 61 to 422 (% males: 55.8 to 86.7). The prevalence of hepatocellular carcinomas ranged between 32.6% to 76.1% on a per lesion basis. The index tests were a CT-scan (16, 64, and/or 128 rows, slice thickness ranging between 0.6-5mm (not reported in 2 studies)) and MRI (1.5T and/or 3T, slice thickness between 2 and 5 (not reported in 4 studies), using gadopentetate dimeglumine (=1) / gadodiamide (n=1) / gadobenate dimeglumine (n=2) / gadobenate dimeglutamine (n=1) / gadolinium diethylene triamine pentaacetic acid (n=1) / gadoterate meglumine (n=1) / gadolinium chelates n=1) / gadolinium (n=1) / extracellular contrast (not specified, n=1)). Acquisition time during the arterial phase ranged from 5 to 40 seconds for CT (not reported by 2 studies) and from 10 to 35 seconds for MrI (not reported in 4 studies). For the portal venous phase, this was 60 to 90 seconds with CT (not reported in 2 studies) and 60 to 80 seconds for MRI (not reported by 3 studies). Diagnosis in the primary studies was based on LI-RADS (v2014, v2018), EASL2001/AASLD 2005, or based on arterial hyper-enhancement/wash-out during the portal venous phase. Authors assessed the risk of bias using the QUADAS-2 tool.

Li (2019) included studies about the diagnostic accuracy of Gd-EOB-DPTA-MRI and MDCT for detecting a hepatocellular carcinoma in suspected patients for their systematic review and meta-analysis. The search was performed on 8 January 2019 in PubMed, Embase and the Cochrane Library with the language limited to English. Studies were included when the diagnostic accuracy of MDCT and Gd-EOB-DPTA-MRI was assessed, the study included more than 30 cases, the reference standard was pathology after liver explant / resection / biopsy or was imaging follow-up, when data was available to construct a 2-by-2 table, the design was prospective, and the article was written in English. Studies were excluded when the design was retrospective, when the participant only had a CT or MRI (instead of both), the publication was a letter, systemic evaluation, literature review, comment, animal model, conference abstract, or written in non-English. Eight studies were included. The authors assessed the studies with the QUADAS-2 tool for their risk of bias. The included studies used CT (16/40/64 rows) and MRI (1.5-3T) and diagnosed hepatocellular carcinomas based on the LI-RADS criteria (n=3), arterial hyperenhancement/washout in the portal venous phase (n=4), or any two positive criteria from a set of five (n=1). Number of patients in the studies

ranged from 33 to 131 (27 to 85 males per study) and the number of lesions in the studies ranged from 48 to 132. Follow-up was at least six months in all studies. Prevalence in the studies, based on the number hepatocellular carcinomas and number of overall lesions, ranged from 53.6% to 100%.

Roberts (2018) performed a systematic review to assess the performance of multiphasic CT-scans compared to multiphasic MR imaging in patients with cirrhosis suspected of hepatocellular carcinomas. The databases Ovid MEDLINE (including Medline In-Process& Other Non-Indexed Citations), EMBASE, Cochrane Central Register of Controlled Trials, and Scopus were searched up to 27 April 2016. Studies were included when they concerned adults with cirrhosis, patients were suspected of a hepatocellular carcinoma, multiphasic CT was compared to MR imaging with and without extracellular contrast or gadoxetate disodium, and the accuracy of identifying or staging a hepatocellular carcinoma was reported. Studies were excluded when they were non-comparative, reviews, case-reports, or had less than five patients included. Study quality was assessed with the QUADAS-2 tool. Nineteen studies were included for the overall analysis comparing contrast-enhanced CT-scans to MR imaging with and without contrast agents. In the sub-analyses, eight studies compared contrast enhanced CT-scans to gadoxetate enhanced MR imaging and eleven studies compared contrast enhanced CT-scans to MR imaging with extracellular contrast agents. Sample sizes of the included studies ranged from 11 to 512. Reported mean or median age in the samples ranged from 46.5 to 67 years (age was not reported in three studies), while the number of lesions in the samples ranged from 17 to 254 (not reported in one study).

Results

Multiphasic CT versus extracellular contrast-enhanced MRI

Both Chen (2022) and Roberts (2018) performed a meta-analysis for a head-to-head comparison of CT and extracellular contrast-enhanced MRI in patients with liver disease. Seven primary studies overlapped in the analysis from both systematic reviews (Chen, 2022; Roberts, 2018). Chen (2022) included three additional studies which were not included in Roberts (2018), and Roberts (2018) included four additional studies not included in Chen (2022).

Sensitivity

Chen (2022) reported an overall pooled sensitivity estimate of 0.63 (95%CI: 0.56 to 0.69, I^2: 81.44%) for CT and 0.77 (95%CI: 0.70 to 0.84, I^2: 82.03%) for MRI from 10 studies. For lesions smaller than 2cm, the pooled sensitivity from 8 studies was 0.60 (95%CI: 0.53-0.67, I^2: 62.43%) for CT and 0.69 (95%CI: 0.60 to 0.76, I^2: 74.74%) for MRI. The sensitivity for lesions larger than 2cm, the pooled sensitivity estimate from 5 studies was 0.79 995%CI: 0.68 to 0.86, I^2: 70.44%) for CT and 0.89 (95%CI: 0.78 to 0.95, I^2: 88.31%) for MRI.

Roberts (2018) reported an overall sensitivity estimate for CT (0.61, 95%CI: 0.54 to 0.87, I^2: 57.77%) and from MR imaging with extracellular contrast agents (0.75, 95%CI: 0.67 to 0.82, I^2: 73.67%). For lesions smaller than one centimeter, the pooled sensitivity estimate from 2 studies was 0.48 for CT (95%CI: 0.32 to 0.62, I^2: 52%) and 0.69 for MRI (95%CI: 0.54 to 0.81, I^2: 94.6%). The pooled sensitivity estimates increased to 0.64 (95%CI: 0.58-0.70, I^2: 61.79%) for CT and to 0.70 (95%CI: 0.64 to 0.75, I^2: 80.4%) for MRI from six studies for lesions between one and two centimeters. For lesions larger than two centimeters (3 studies), the sensitivity estimates further increased to 0.79 for CT (95%CI: 0.70 to 0.86, I^2: 88.2%) and to 0.88 for MRI (95%CI: 0.80 to 0.93, I^2: 70.5%).

Specificity

Chen (2022) performed a meta-analysis with 10 studies and reported an overall specificity estimate of 0.93 (95%CI: 0.85 to 0.96, I^2: 75.79%) for CT and 0.94 (95%CI: 0.81 to 0.98, I^2: 92.95%) for MRI. The pooled specificity estimate for lesions smaller than 2cm was 0.92 (95%CI: 0.79 to 0.97, I^2: 82.42%) for CT and 0.94 (95%CI: 0.73 to 0.99, I^2: 93.14%) for MRI, using 8 studies. The meta-analysis, containing 5 studies, for lesions larger than 2cm showed a pooled specificity of 0.92 (95%CI: 0.83 to 0.96, I^2:0%) for CT and 0.93 (95%CI: 0.82 to 0.97, I^2: 46.96%) for MRI.

Roberts (2018) reported an overall specificity estimate for CT (0.87, 95%CI: 0.73 to 0.94, I^2: 84.84%) and for MR imaging with extracellular contrast agents (0.86, 95%CI: 0.68 to 0.95, I^2: 90.04%). For lesions smaller than one centimeter, the pooled specificity estimate from 2 studies was 0.69 for CT (95%CI: 0.51 to 0.83, I^2: 0%) and 0.46 for MRI (95%CI: 0.29 to 0.63, I^2: 84.3%). The pooled specificity estimates increased to 0.88 (95%CI: 0.82 to 0.92, I^2: 90.89%) for CT and to 0.87 (95%CI: 0.81 to 0.91, I^2: 92.1%) for MRI from six studies for lesions between one and two centimeters. For lesions larger than two centimeters (3 studies), the specificity estimates were 0.90 for CT (95%CI: 0.76 to 0.97, I^2: 0%) and to 0.87 for MRI (95%CI: 0.73 to 0.96, I^2: 0%).

Positive predictive value

Not reported.

Negative predictive value

Not reported.

Area under the curve (AUC)

Chen (2022) calculated the AUC for both CT and MRI. The AUC was calculated for overall diagnosis with CT (AUC: 0.80, 95%CI: 0.76 to 0.83), for lesions smaller than 2cm with CT (AUC: 0.72, 95%CI: 0.68 to 0.76), and for lesions larger than 2cm with CT (AUC: 0.93, 95%CI: 0.91 to 0.95). For MRI, the AUC was 0.88 (95%CI: 0.85 to 0.91), 0.79 (95%CI: 0.76 to 0.83), 0.96 (95%CI: 0.94 to 0.98) respectively.

Costs

Not reported.

Multiphasic CT versus gadoxetate enhanced MRI

Both Li (2019) and Roberts (2018) performed head-to-head meta-analyses for CT versus gadoxetate enhanced MRI. One primary study overlapped in the body of evidence in the systematic reviews and was both included by Li (2019) and by Roberts (2018). The remaining studies did not overlap.

Sensitivity

Li (2019) reported a pooled overall sensitivity estimate for CT of 0.68 (95%CI: 0.51 to 0.81) and for MRI 0.85 (95%CI: 0.77 to 0.90). For detecting hepatocellular carcinomas smaller than two centimeters, Li (2019) reported a pooled sensitivity estimate of 0.46 (95%CI: 0.32 to 0.61) for CT and 0.79 (0.67 to 0.87) for MRI. A pooled sensitivity estimate for detecting hepatocellular carcinomas smaller than two centimeters was not provided, however the sensitivities from the individual studies ranged from 0.00 (95%CI: 0.00 to 0.52) to 0.82 (95%CI: 0.65 to 0.93) for CT and from 0.00 (95%CI: 0.00 to 0.52) to 0.84 (95%CI: 0.67 to 0.95) for MRI.

Roberts (2018) found a pooled sensitivity of 0.73 (95%CI: 0.64 to 0.81, I^2: 76.35%) for CT and 0.87 (95%CI: 0.79 to 0.93, I^2: 78.12%) for MRI. The sensitivity of CT decreased to 0.68 (95%CI: 0.55 to 0.79, I^2: 23.2%) and of MRI to 0.76 (95%CI: 0.67 to 0.84, I^2: 0%) for lesions smaller than 2 centimeters (from 2 studies).

Specificity

Li (2019) found a summary estimate of the overall specificity for CT of 0.92 (95%CI: 0.84 to 0.96) and 0.94 for MRI (95%CI: 0.88 to 0.97). For detecting hepatocellular carcinomas smaller than two centimeters, the summary specificity was 0.93 (95%CI: 0.83 to 0.97) for CT and 0.92 for MRI (95%CI: 0.77 to 0.97). Studies for hepatocellular carcinomas larger than two centimeters were not pooled and specificities ranged from 0.00 (95%CI: 0.00 to 0.84) to 1.00 (95%CI: 0.16 to 1.00) for CT. All three studies reported a specificity of 1.00 for MRI with the lower border of the 95% confidence interval ranging from 0.16 to 0.29.

Roberts (2018) reported a specificity of 0.96 (95%CI: 0.90 to 0.97, I^2: 80.31%) for CT and 0.94 (95%CI: 0.90 to 0.97, I^2: 60.07%) for MRI. For lesions smaller than two centimeters, the specificity increased to 0.98 (95%CI: 0.90 to 1.00, I^2: 13.3%) for CT and to 0.96 (95%CI: 0.87 to 0.99, I^2: 0%) for MRI from 2 studies.

Positive predictive value

Not reported.

Negative predictive value

Not reported.

Area under the curve

Li (2019) reported the overall AUC of CT (AUC: 0.91, 95%CI: 0.88 to 0.93) and of MRI (AUC: 0.96, 95%CI: 0.94 to 0.97). For lesions smaller than two centimeters, the AUC was 0.82 (95%CI: 0.78 to 0.85) for CT and 0.90 (95%CI: 0.87 to 0.93) for MRI.

Costs

Not reported.

Level of evidence of the literature

Multiphasic CT versus extracellular contrast-enhanced MRI

The level of evidence regarding the outcome measure sensitivity was downgraded by 2 levels because of study limitations (1 level risk of bias: about half of the studies were judged to be at high or unclear risk for introducing bias on the flow and timing domain (including studies with large sample sizes)); conflicting results (1 level for inconsistency: estimates seem to vary with confidence intervals not sufficiently overlapping when eyeballing the forest plots, I^2 indicates heterogeneity); number of included patients (imprecision not downgraded: already downgraded for heterogeneity where the heterogeneity could introduce larger confidence intervals for the pooled estimates); publication bias (not downgraded for publication bias: Chen (2022) suggested there was no publication bias; Roberts (2018) suggested there was publication bias, however we judged their funnel plot to be symmetrical enough) .

The level of evidence regarding the outcome measure specificity was downgraded by 2 levels because of study limitations (1 level risk of bias: about half of the studies were judged to be at high or unclear risk for introducing bias on the flow and timing domain (including studies with large sample sizes)); conflicting results (1 level for inconsistency: estimates

seem to vary with confidence intervals not sufficiently overlapping when eyeballing the forest plots, I^2 indicates heterogeneity); number of included patients (imprecision not downgraded: already downgraded for heterogeneity where the heterogeneity could introduce larger confidence intervals for the pooled estimates); publication bias (not downgraded for publication bias: Chen (2022) suggested there was no publication bias; Roberts (2018) suggested there was publication bias, however we judged their funnel plot to be symmetrical enough) .

The level of evidence regarding the outcome measure positive predictive value and negative predictive value could not be graded, since none of the included studies reported these outcomes.

The level of evidence regarding the outcome measure area under the curve was downgraded by 1 level because of study limitations (1 level risk of bias: about half of the studies were judged to be at high or unclear risk for introducing bias on the flow and timing domain (including studies with large sample sizes)); number of included patients; publication bias (not downgraded for publication bias: Chen (2022) suggested there was no publication bias; Roberts (2018) suggested there was publication bias, however we judged their funnel plot to be symmetrical enough).

The level of evidence regarding the outcome measure costs could not be graded since none of the included studies reported this outcome.

Multiphasic CT versus gadoxetate enhanced MRI

The level of evidence regarding the outcome measure sensitivity was downgraded by 2 levels because of study limitations (1 level for risk of bias: Roberts (2018) judged 5/8 studies to have high or unclear risk of bias on patient selection and 4/8 high or unclear risk on flow and timing; Li (2019) judged 2/8 to be high or unclear risk on patient selection and 2/8 high risk on index test; overall there seems to be concerns mostly about patient selection); conflicting results (1 level for inconsistency: eyeballing the plots the estimates seem to vary and the confidence intervals may not overlap sufficiently, the I^2 was considered to be large for the overall analyses (Roberts, 2018 provided the I^2)); number of included patients (imprecision was not downgraded as heterogeneity could have caused the wide intervals); publication bias (not downgraded for publication bias: Roberts (2018) suggested there was publication bias, however we judged their funnel plot to be symmetrical enough. Li (2019) performed the Deek's funnel plot asymmetry test and found no evidence of publication bias).

The level of evidence regarding the outcome measure specificity was downgraded by 2 levels because of study limitations (1 level for risk of bias: Roberts (2018) judged 5/8 studies to have high or unclear risk of bias on patient selection and 4/8 high or unclear risk on flow and timing; Li (2019) judged 2/8 to be high or unclear risk on patient selection and 2/8 high risk on index test; overall there seems to be concerns mostly about patient selection); conflicting results (1 level for inconsistency: eyeballing the plots the estimates seem to vary and the confidence intervals may not overlap sufficiently, the I^2 was considered to be large for the overall analyses (Roberts, 2018 provided the I^2)); number of included patients (imprecision was not downgraded as heterogeneity could have caused the wide intervals); publication bias (not downgraded for publication bias: Roberts (2018) suggested there was publication bias, however we judged their funnel plot to be symmetrical enough. Li (2019) performed the Deek's funnel plot asymmetry test and found no evidence of publication bias).

The level of evidence regarding the outcome measure positive predictive value and negative predictive value could not be graded, since none of the included studies reported these outcomes.

The level of evidence regarding the outcome measure area under the curve was downgraded by 1 level because of study limitations (1 level for risk of bias; Li (2019) judged 2/8 to be high or unclear risk on patient selection, 2/8 high risk on index test. 3/8 unclear on reference test and 2/8 unclear on flow and timing); publication bias (not downgraded for publication bias: Li (2019) performed the Deek's funnel plot asymmetry test and found no evidence of publication bias).

The level of evidence regarding the outcome measure costs could not be graded since none of the included studies reported this outcome.

Conclusions

Multiphasic CT versus extracellular contrast-enhanced MRI

Low GRADE	There is a low confidence in the reported sensitivities of CT compared to extracellular contrast-enhanced MRI, however MRI might have a somewhat higher sensitivity than CT in patients with liver cirrhosis suspected of a hepatocellular carcinoma. The sensitivity for both CT and MRI might increase with an increasing lesion size, but certainty decreases with larger confidence intervals. *Sources: (Roberts, 2018; Chen, 2022)*

Low GRADE	There is a low confidence in the reported specificities of CT compared to extracellular contrast-enhanced MRI in patients with cirrhosis suspected of a hepatocellular carcinoma. Overall, the specificity of CT might be similar to extracellular contrast-enhanced MRI. *Sources: (Roberts, 2018; Chen, 2022)*

- GRADE	No studies were included that reported the positive or negative predictive values of CT compared to extracellular contrast-enhanced MRI in patients with cirrhosis suspected of a hepatocellular carcinoma.

Moderate GRADE	There is a moderate confidence in the reported area under the curve of CT compared to extracellular contrast-enhanced MRI in patients with cirrhosis suspected of a hepatocellular carcinoma. Extracellular contrast-enhanced MRI could have a somewhat larger area under the curve than CT. The area under the curve for both CT and MRI might increase with an increasing lesion size. *Sources: (Chen, 2022)*

- GRADE	No studies were included that reported the costs of CT compared to extracellular contrast-enhanced MRI in patients with cirrhosis suspected of a hepatocellular carcinoma.

Multiphasic CT versus gadoxetate enhanced MRI

Low GRADE	There is a low confidence in the reported sensitivities of CT compared to gadoxetate enhanced MRI in patients suspected of a hepatocellular carcinoma. However, MRI might have a somewhat higher sensitivity than CT. Sensitivity may decrease when the lesion is smaller than two centimeters. *Sources: (Roberts, 2018; Li, 2019)*

Low GRADE	There is a low confidence in the reported specificities of CT compared to gadoxetate enhanced MRI in patients suspected of a hepatocellular carcinoma. Both MRI and CT might be somewhat comparable. *Sources: (Roberts, 2018; Li, 2019)*

- GRADE	No studies were included that reported the positive or negative predictive values of CT compared to gadoxetate enhanced MRI in patients suspected of a hepatocellular carcinoma.

Moderate GRADE	There is a moderate confidence in the reported area under the curve of CT compared to gadoxetate enhanced MRI in patients suspected of a hepatocellular carcinoma. Gadoxetate enhanced MRI could have a somewhat larger area under the curve than CT. *Sources: (Li, 2019)*

- GRADE	No studies were included that reported the costs of CT compared to gadoxetate enhanced MRI in patients suspected of a hepatocellular carcinoma.

Overwegingen - van bewijs naar aanbeveling

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

Drie systematische reviews werden geïncludeerd (Roberts, 2018; Li, 2019; Chen, 2022). Voor de vergelijking van multi-fase CT ten opzichte van MRI met extracellulaire contrastvloeistof includeerden Roberts (2018) en Chen (2022) voor een deel dezelfde studies. Beide systematische literatuuronderzoeken includeerden patiënten met levercirrose. Zowel Roberts (2018) als Chen (2022) includeerden ook primaire studies die niet door de ander werden geïncludeerd en voerden hier meta-analyses mee uit. Beide systematische literatuuronderzoeken werden daarom besproken hoewel er een grote overlap bestaat. Met een lage zekerheid, veroorzaakt door een risico op vertekening en de heterogeniteit tussen de primaire studies, lijkt MRI met extracellulair contrastmiddel een wat hogere sensitiviteit te kunnen hebben dan de CT-scan. De specificiteit zou mogelijk gelijkwaardig kunnen zijn tussen beide modaliteiten. Echter rapporteerde Roberts (2018) een hogere specificiteit voor CT-scans bij laesies kleiner dan één centimeter, maar dit betreft data uit slechts twee primaire studies. Het gebied onder de curve (AUC, area under the curve) is mogelijk iets groter voor MRI met extracellulair contrastmiddel, maar relatief vergelijkbaar met CT-scans. Over het algemeen lijkt het patroon te ontstaan, voor zowel de CT-scan als MRI met extracellulair contrastmiddel, dat laesies moeilijker te classificeren lijken naar mate deze kleiner zijn.

Twee systematische literatuuronderzoeken vergeleken de prestaties van multi-fase CT-scans ten opzichte van MRI met gadoxetaat contrastmiddel (Roberts, 2018; Li, 2019). De

geïncludeerde literatuur in beide systematische literatuuronderzoeken overlapte slechts met één primaire studie. Beide systematische literatuuronderzoeken bevatten ook meta-analyses. Met lage zekerheid, door een risico op vertekening en de heterogeniteit tussen de primaire studies, lijkt MRI met gadoxetaat contrastmiddel een hogere sensitiviteit te kunnen hebben dan de CT-scan en mogelijk een vergelijkbare specificiteit. Het gebied onder de curve (AUC) is mogelijk voor MRI met gaxodetaat wat groter dan voor CT-scans. Ook in deze vergelijking lijkt het patroon te ontstaan dat kleinere laesies door zowel CT-scans als MRI met gadoxetaat contrastmiddelen moeilijker te classificeren lijken dan grotere laesies.

De prestaties van CT en MRI werden in een hypothetisch cohort berekend op verschillende prevalenties van patiënten met een hepatocellulair carcinoom, zie Tabel 2.1.

Tabel 2.1 Classificaties van CT en MRI in een hypothetisch cohort van n=1000 berekend aan de hand van de gerapporteerde algehele gepoolde schatters van de sensitiviteit en specificiteit uit de systematische literatuuronderzoeken (Chen, 2022; Li, 2019; Roberts, 2018). Voor de berekening werd een prevalentie van 30%, 50% en 70% in het hypothetische cohort gebruikt.

	Prevalentie: 30%		**Prevalentie: 50%**		**Prevalentie: 70%**	
Classificatie	***CT***	***MRI***	***CT***	***MRI***	***CT***	***MRI***
CT versus MRI (extracellulair contrast)						
- Chen 2022						
Terecht positief	189 (95%CI: 168-207)	231 (95%CI: 210-252)	315 (95%CI: 280-345)	385 (95%CI: 350-420)	441 (95%CI: 392-483)	539 (95%CI: 490-588)
Fout positief	49 (95%CI: 35-105)	42 (95%CI: 14-133)	35 (95%CI: 25-75)	30 (95%CI: 10-95)	21 (95%CI: 15-45)	18 (95%CI: 6-57)
Fout negatief	111 (95%CI: 93-132)	69 (95%CI: 48-90)	185 (95%CI: 155-220)	115 (95%CI: 80-150)	259 (95%CI: 217-308)	161 (95%CI: 112-210)
Terecht negatief	651 (95%CI: 595-665)	658 (95%CI: 567-686)	465 (95%CI: 425-475)	470 (95%CI: 405-490)	279 (95%CI: 255-285)	282 (95%CI: 243-294)
- Roberts 2018						
Terecht positief	183 (95%CI: 162-261)	225 (95%CI: 201-246)	305 (95%CI: 270-435)	375 (95%CI: 335-410)	427 (95%CI: 378-609)	525 (95%CI: 469-574)
Fout positief	91 (95%CI: 42-189)	98 (95%CI: 35-224)	65 (95%CI: 30-135)	70 (95%CI: 25-160)	39 (95%CI: 18-81)	42 (95%CI: 15-96)
Fout negatief	117 (95%CI: 39-138)	75 (95%CI: 54-99)	195 (95%CI: 65-230)	125 (95%CI: 90-165)	273 (95%CI: 91-322)	175 (95%CI: 126-231)
Terecht negatief	609 (95%CI: 511-658)	602 (95%CI: 476-665)	435 (95%CI: 365-470)	430 (95%CI: 340-475)	261 (95%CI: 219-282)	258 (95%CI: 204-285)
CT versus MRI (gadoxetaat contrast)						
- Li 2019						
Terecht positief	204 (95%CI: 153-243)	255 (95%CI: 231-270)	340 (95%CI: 255-405)	425 (95%CI: 385-450)	476 (95%CI: 357-567)	595 (95%CI: 539-630)
Fout positief	56 (95%CI: 28-112)	42 (95%CI: 21-84)	40 (95%CI: 20-80)	30 (95%CI: 15-60)	24 (95%CI: 12-48)	18 (95%CI: 9-36)
Fout negatief	96 (95%CI: 57-147)	45 (95%CI: 30-69)	160 (95%CI: 95-245)	75 (95%CI: 50-115)	224 (95%CI: 133-343)	105 (95%CI: 70-161)
Terecht negatief	644 (95%CI: 588-672)	658 (95%CI: 616-679)	460 (95%CI: 420-480)	470 (95%CI: 440-485)	276 (95%CI: 252-288)	282 (95%CI: 264-291)

- Roberts 2018						
Terecht positief	219 (95%CI: 192-243)	261 (95%CI: 237-279)	365 (95%CI: 320-405)	435 (95%CI: 395-465)	511 (95%CI: 448-567)	609 (95%CI: 553-651)
Fout positief	28 (95%CI: 21-70)	42 (95%CI: 21-70)	20 (95%CI: 15-50)	30 (95%CI: 15-50)	12 (95%CI: 9-30)	18 (95%CI: 9-30)
Fout negatief	81 (95%CI: 57-108)	39 (95%CI: 21-63)	135 (95%CI: 95-180)	65 (95%CI: 35-105)	189 (95%CI: 133-252)	91 (95%CI: 49-147)
Terecht negatief	672 (95%CI: 630-679)	658 (95%CI: 630-679)	480 (95%CI: 450-485)	470 (95%CI: 450-485)	288 (95%CI: 270-291)	282 (95%CI: 270-291)

Twee Cochrane reviews voerden meta-analyses uit voor CT (Nadarevic, 2021) en MRI (Nadarevic, 2022) afzonderlijk voor de detectie van hepatocellulair carcinomen van elke grootte en stadium bij volwassen patiënten met chronische leveraandoeningen, zonder een directe vergelijking tussen de modaliteiten. Voor CT werd een gepoolde sensitiviteit van 0,78 (95%BHI: 0,71 tot 0,83) en een specificiteit van 0,91 (95%BHI: 0,87 tot 0,95) gerapporteerd (Nadarevic, 2021). Voor MRI werd een sensitiviteit van 0,84 (95%BHI: 0,80-0,88) en een specificiteit van 0,94 (95%BHI: 0,90 tot 0,96) gerapporteerd (Nadarevic, 2022). De auteurs in beide Cochrane reviews beoordeelden het vertrouwen in de resultaten als 'laag'. Deze resultaten en beoordelingen lijken in lijn te zijn met de geïncludeerde systematische literatuuronderzoeken die CT en MRI met elkaar direct hebben kunnen vergelijken.

Op basis van de geïncludeerde literatuur zijn er slechts indirecte vergelijkingen te maken voor het type contrastmiddel voor MRI. Bij deze indirecte vergelijking lijkt MRI met gadoxetaatzuur over het algemeen een hogere accuratesse te hebben dan een extracellulair contrast (Chen, 2022; Li, 2019; Roberts, 2018). Door de indirecte vergelijking neemt de zekerheid in het bewijs af en is het moeilijk om op basis van de gerapporteerde accuratesse parameters een uitspraak te doen over welk contrastmiddel de voorkeur geniet. De parameters zouden bijvoorbeeld kunnen variëren door verschillen in de studieopzet, setting en voorgaande testen, of verschillende karakteristieken in de steekproeven. Er is daardoor een directe vergelijking nodig binnen prospectieve cohorten die een case-control opzet vermijden om voor directe data te zorgen. De European Association for the Study of the Liver (EASL) stelt in haar richtlijn dat prospectieve studies met een directe vergelijking lijken te ontbreken (Galle, 2018). De zoekvraag in de huidige module zette CT af tegen MRI, waardoor er niet specifiek gezocht werd naar studies die de MRI-contrastmiddelen head-to-head vergeleken. Er is daardoor geen zekerheid dat er geen prospectieve studies zijn over dit onderwerp, in het bijzonder over eventuele studies die na de EASL richtlijn verschenen zouden kunnen zijn.

Het 'Liver Reporting & Data System (LI-RADS) is een beknopt systeem ontwikkeld door een multidisciplinair team, te gebruiken bij de standaardisatie van de data-collectie, interpretatie en verslaglegging van bevindingen op leverbeeldvorming (American College of Radiology, 2018; Elmohr, 2021). Dit categorisatie-systeem wordt specifiek toegepast bij patiënten met risicofactoren op het ontwikkelen van een hepatocellulair carcinoom, zoals cirrose, chronische hepatitis B of een voorgeschiedenis met een eerder hepatocellulair carcinoom (American College of Radiology, 2018). Er zijn 2 categorisatie systemen, namelijk voor CT/MRI en voor contrastechografie. Het algoritme maakt onderscheid in de classificering van onbehandelde observaties zonder pathologisch bewijs bij patiënten met een hoge kans op een hepatocellulair carcinoom (American College of Radiology, 2018; Elmohr, 2021). Het CT/MRI LI-RADS algoritme categoriseert observaties in waarschijnlijkheidsniveaus waarin een hepatocellulair carcinoom aanwezig zou kunnen zijn. Deze variëren van LR-1 (zeker

benigne) tot LR-5 (zeker een hepatocellulair carcinoom). Er bestaan ook categorieën voor niet-categoriseerbaar (LR-NC), waarschijnlijk of zeker maligne maar niet noodzakelijk een hepatocellulair carcinoom (LR-M) en een zekere ingroei van de tumor in een ader (LR-TIV). De diagnose is gebaseerd op verschillende combinaties van 5 belangrijke kenmerken en verschillende bijkomstige kenmerken. De hoofdkenmerken zijn: aanwezigheid van verhoogde aankleuring in de arteriële fase (niet ringvormig), non-perifere wash-out, grootte van de laesie, capsulaire aankleuring, en toename in grootte tussen opeenvolgende onderzoeken (>50% groei in <6maanden). De bijkomstige kenmerken worden opgedeeld in 3 groepen: algemene kenmerken die pleiten voor maligniteit, algemene kenmerken die pleiten voor HCC en algemene kenmerken die pleiten voor benigniteit. Het algoritme én de exacte indeling van de categorieën zijn terug te vinden in de LI-RADS CT/MRI beschrijving, zie hiervoor de meest recente versie op de website van de American College of Radiology.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

Het onderzoek met MRI duurt langer dan een CT-scan. Voor MRI is de duur ongeveer 30 minuten, tegenover ongeveer 10 minuten voor een CT-scan. Het voordeel van MRI is dat er geen gebruik wordt gemaakt van ioniserende straling. Het contrastmiddel dat voor MRI's gebruikt wordt is daarnaast ook minder nefrotoxisch in vergelijking met de CT-scan, maar wel belastender voor het milieu. Het is belangrijk dat de beeldvorming een hoge kans op een terecht positieve classificatie heeft wanneer de ziekte daadwerkelijk aanwezig is en daarmee ook weinig fout-negatieve classificaties geeft.

Kosten (middelenbeslag)

Vanuit de geïncludeerde systematische literatuuronderzoeken in de literatuuranalyse werden er geen gegevens gevonden over de kosten(effectiviteit) voor de vergelijking tussen CT en MRI.

Aanvaardbaarheid, haalbaarheid en implementatie

Iedere patiënt heeft mogelijke toegang tot MRI en CT, maar de beschikbaarheid van MRI is eventueel een moeilijkheid. Een MRI duurt langer en is iets duurder dan een CT, maar heeft daarentegen geen ioniserende staling en is minder nefrogeen belastend. Er zijn in deze context geen subgroepen bekend waar andere overwegingen voor zouden gelden met betrekking tot de aanvaardbaarheid en implementatie. Het uitvoeren en interpreteren van een MRI lever is tevens basiskennis voor abdominale radiologen. Het lijkt daarom aannemelijk dat een MRI lever te implementeren is in de praktijk bij voldoende beschikbaarheid van MRI.

Aanbevelingen

Aanbeveling-1

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

Voor de diagnose van HCC bij patiënten met levercirrose lijkt de sensitiviteit van MRI hoger te zijn dat die van CT, met vergelijkbare specificiteit. De sensitiviteit van beeldvorming voor de diagnose van HCC is lager bij kleine laesies (<10mm en 11-20mm). Door de indirecte vergelijking tussen studies die opgenomen zijn in de literatuuranalyse lijkt het verkiezen van een constrastmiddel voor MRI boven een ander contrastmiddel op basis van de accuratesse op dit moment nog onvoldoende onderbouwd te zijn. De kosten van het leverspecifiek constrastmiddel zijn veel hoger dan het extra-cellulair Gadolinium contrastmiddel.

Overweeg bij patiënten met cirrose met verdenking van HCC die op de echo is gezien bij de primaire diagnostiek MRI met contrast toe te passen in plaats van CT.

- Gezien de kosten is er een voorkeur voor extracellulair gadolinium boven leverspecifiek contrast. Indien de MRI technisch, bijvoorbeeld door implantaten, of vanuit patiëntenoogpunt (bv. claustrofobie), niet mogelijk is, kan dit vervangen worden door CT.
- Wanneer de diagnose van HCC is gesteld met CT, is er alleen aanvullend MRI nodig wanneer er consequenties worden verwacht ten aanzien van het beleid.

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Kennislacunes

What is the diagnostic accuracy of a CT-scan (using a dedicated liver scan protocol) compared to MR imaging (using a dedicated liver MRI scan protocol) in patients with a focal liver lesion suspected of a hepatocellular carcinoma?

What is the diagnostic accuracy of gadoxetate enhanced MRI compared to extracellular enhanced MRI in patients with a focal liver lesion suspected of a hepatocellular carcinoma?

Evidence tables

Evidence table for systematic reviews of diagnostic test accuracy studies

Research question:

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Chen 2023 Study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis) *Literature search up to 01/05/2021* **A**: Golfieri 2009 **B**: Hassan 2011 **C**: Khalili 2011 **D**: Martion 2013 **E**: Basha 2018 **F**: Min 2019 **G**: Ronot 2017 **H**: Leoni 2010 **I**: Sangiovanni 2010 **J:** Serste 2012 <u>Study design</u>: cohort, case-control	Inclusion criteria SR: diagnostic performance of ECA-MRI and CE-CT in patients with chronic liver disease for diagnosing HCC, HCC was diagnosed on pathological evidence and/or imaging follow-up of at least 6 months, data for head-to-head comparison was sufficient to construct a 2x2 table, articles could be retrieved, Exclusion criteria SR: accuracy of ECA-MRI and CE-CT were not assessed, conference abstracts / case reports / commentary / letter / review or meta-analysis and	Describe index and comparator tests* and cut-off point(s): A-1: CT 16 (slice thickness: 5 mm, arterial phase: 10–14 sec, portal venous phase: 70, criteria: EASL 2001/AASLD) A-2: MRI 1.5T, (slice thickness: 2–2.5 mm, contrast: Gadopentetate dimeglumine, arterial phase: 10–14 sec, portal venous phase: 60–80, criteria: EASL 2001/AASLD) B-1: CT 64 (slice thickness: NA mm, arterial phase: NA sec, portal venous phase: NA, criteria: Ar)	Describe reference test and cut-off point(s): A: pathology on excision/biopsy B: pathology on biopsy or imaging follow-up C: pathology on biopsy or imaging follow-up D: pathology on excision/biopsy or imaging follow-up E: pathology on biopsy or imaging follow-up F: pathology on excision/biopsy or imaging follow-up	Endpoint of follow-up: NA	Outcome measures and effect size (include 95%CI and p-value if available): <u>Overall sensitivity CT versus. ECA-MRI (95%CI):</u> A-1: CT: 0.62 (95%CI: 0.51-0.72) A-2: ECA-MRI: 0.81 (95%CI: 0.67-0.91) B-1: CT: 0.62 (95%CI: 0.42-0.79) B-2: ECA-MRI: 0.90 (95%CI: 0.74-0.91) C-1: CT: 0.53 (95%CI: 0.35-0.70)	<u>Study quality (ROB):</u> Assessed with QUADAS-2 Hassan 2011 and Golfieri 2009 at high risk of bias. Ronot 2017 unclear risk.

	(prospective / retrospective) **A:** prospective **B**: retrospective **C**: retrospective **D**: prospective **E**: prospective **F**: prospective **G**: prospective **H**: retrospective **I**: prospective **J:** retrospective <u>Setting and Country</u>: **A:** Italy **B**: Egypt **C**: Canada **D**: Italy **E**: Egypt **F**: South Korea **G**: France **H**: Italy **I**: Italy **J:** France <u>Source of funding and conflicts of interest:</u> Authors declare they have no conflicts of interest (not reported for individual studies)	other special types of work, no head-to-head comparison *10 studies included* <u>Important patient characteristics</u>: *Number of patients; characteristics important to the research question; for example, age, sex, bmi, ...* <u>N</u> **A: 63** **B**: 61 **C**: 84 **D**: 140 **E**: 240 **F**: 125 **G**: 422 **H**: 60 **I**:64 **J:** 74 <u>*Sex (% male)*</u>*:* **A:** 84.1% **B**: 60.7% **C**: 63.1% **D**: 74.3% **E**: 55.8% **F**: 81.6% **G**: 81.3% **H**: 86.7% **I**: 73.4% **J:** 78.4%	B-2: MRI 1.5T, (slice thickness: NA mm, contrast: Gadodiamide, arterial phase: NA sec, portal venous phase: NA, criteria: Ar) C-1: CT 64 (slice thickness: 2.5–5 mm, arterial phase: 20 sec, portal venous phase: 60, criteria: EASL 2001/AASLD) C-2: MRI 1.5T, (slice thickness: NA mm, contrast: Gadobenate dimeglumine, arterial phase: NA sec, portal venous phase: NA, criteria: EASL 2001/AASLD) D-1: CT 64 (slice thickness: 3–5 mm, arterial phase: 25–40 sec, portal venous phase: 70, criteria: Ar) D-2: MRI 1.5T, (slice thickness: 3–5 mm, contrast: Gadobenate dimeglumine, arterial phase: 22–35 sec, portal venous phase: 70, criteria: Ar) E-1: CT 64/128 (slice thickness: 5 mm, arterial phase: 18 sec, portal venous phase: 70, criteria: LI-RADS v 2014) E-2: MRI 1.5T, (slice thickness: 5 mm, contrast: Gadolinium diethylene triamine, arterial phase: 30	G: pathology on excision/biopsy or imaging follow-up H: pathology on biopsy I: pathology on biopsy J: pathology on biopsy Prevalence (%) (based on refence test at specified cut-off point) **A: 70.7%** **B**: 32.6% **C**: 33.7% **D**: 64.2% **E**: 64.9% **F**: 76.1% **G**: 61.2% **H**: 73.3% **I**: 65.7% **J:** 63.5%		C-2: ECA-MRI: 0.62 (95%CI: 0.44-0.78) D-1: CT: 0.72 (95%CI: 0.64-0.79) D-2: ECA-MRI: 0.87 (95%CI: 0.81-0.92) E-1: CT: 0.45 (95%CI: 0.38-0.52) E-2: ECA-MRI: 0.73 (95%CI: 0.67-0.80) F-1: CT: 0.64 (95%CI: 0.55-0.72) F-2: ECA-MRI: 0.83 (95%CI: 0.75-0.0.89) G-1: CT: 0.70 (95%CI: 0.64-0.74) G-2: ECA-MRI: 0.73 (95%CI: 0.67-0.80) H-1: CT: 0.67 (95%CI: 0.53-0.76) H-2: ECA-MRI: 0.82 (95%CI: 0.69-0.91) I-1: CT: 0.44 (95%CI: 0.27-0.62) I-2: ECA-MRI: 0.44 (95%CI: 0.27-0.62) J-1: CT: 0.74 (95%CI: 0.60-0.86) J-2: ECA-MRI: 0.81 (95%CI: 0.67-0.91) Pooled characteristic ('type of statistical analysis' e.g.	

			sec, portal venous phase: 60, criteria: LI-RADS v 2014) F-1: CT 64/128 (slice thickness: 3 mm, arterial phase: 30–40 sec, portal venous phase: 70, criteria: LI-RADS v 2018) F-2: MRI 3.0T, (slice thickness: 2–6 mm, contrast: pentaacetic acid, arterial phase: 25–30 sec, portal venous phase: 60, criteria: LI-RADS v 2018) G-1: CT 16/64 (slice thickness: 0.6–3 mm, arterial phase: 30–35 sec, portal venous phase: 70–, criteria: LI-RADS v 2014) G-2: MRI 1.5/3.0T, (slice thickness: NA mm, contrast: Gadoterate meglumine, arterial phase: NA sec, portal venous phase: 70, criteria: LI-RADS v 2014) H-1: CT 16 (slice thickness: 5 mm, arterial phase: 5 sec, portal venous phase: 70, criteria: EASL 2001/AASLD) H-2: MRI 3.0T, (slice thickness: 2–2.5 mm, contrast: Gadolinium chelates, arterial phase: 18 sec, portal venous phase: 80, criteria: EASL 2001/AASLD) I-1: CT 64 (slice thickness: 2.5 mm, arterial phase: 40			bivariate analysis) per index test and cut-off point: **Index test-1 (cut-off= ..)** 0.63 (95% CI 0.56 to 0.69) Heterogeneity (reasons): 81.44% **Index test-2 (cut-off= ..)** 0.77 (95%CI 0.70-0.91) Heterogeneity: 82.03% <u>Overall specificity CT versus. ECA-MRI (95%CI):</u> A-1: CT: 0.55-0.86 (95%CI: 0.55-0.86) A-2: ECA-MRI: 0.20-0.53 (95%CI: 0.20-0.53) B-1: CT: 0.72-0.91 (95%CI: 0.72-0.91) B-2: ECA-MRI: 0.77-0.94 (95%CI: 0.77-0.94) C-1: CT: 0.92-1.00 (95%CI: 0.92-1.00) C-2: ECA-MRI: 0.95-1.00 (95%CI: 0.95-1.00) D-1: CT: 0.78-0.93 (95%CI: 0.78-0.93)	

			sec, portal venous phase: 80, criteria: AASLD 2005) I-2: MRI 1.5T, (slice thickness: 3 mm, contrast: Gadolinium, arterial phase: 30 sec, portal venous phase: 80, criteria: AASLD 2005) J-1: CT 16 (slice thickness: NA mm, arterial phase: NA sec, portal venous phase: NA, criteria: AASLD 2005) J-2: MRI 1.5T, (slice thickness: NA mm, contrast: Gadobenate dimeglutamine, arterial phase: NA sec, portal venous phase: NA, criteria: AASLD 2005) (use the format 'character+number' if 2 or more index tests are being compared, e.g. A-1, A-2, etc)			D-2: ECA-MRI: 0.83-0.96 (95%CI: 0.83-0.96) E-1: CT: 0.93-1.00 (95%CI: 0.93-1.00) E-2: ECA-MRI: 0.84-0.96 (95%CI: 0.84-0.96) F-1: CT: 0.87-1.00 (95%CI: 0.87-1.00) F-2: ECA-MRI: 0.87-1.00 (95%CI: 0.87-1.00) G-1: CT: 0.83-0.92 (95%CI: 0.83-0.92) G-2: ECA-MRI: 0.85-0.94 (95%CI: 0.85-0.94) H-1: CT: 0.68-0.99 (95%CI: 0.68-0.99) H-2: ECA-MRI: 0.75-1.00 (95%CI: 0.75-1.00) I-1: CT: 0.84 - 1.00 (95%CI: 0.84 - 1.00) I-2: ECA-MRI: 0.84-1.00 (95%CI: 0.84-1.00) J-1: CT: 0.62 - 0.94 (95%CI: 0.62 - 0.94) J-2: ECA-MRI: 0.66-0.96 (95%CI: 0.66-0.96)	

						Pooled characteristic ('type of statistical analysis' e.g. bivariate analysis) per index test and cut-off point: **Index test-1 (cut-off= ..)** 0.93 (95% CI 0.85 to 0.96) Heterogeneity (reasons): 75.79% **Index test-2 (cut-off= ..)** 0.94 (95%CI: 0.81-0.98) Heterogeneity: 92.95% <u>Sensitivity HCC<2cm CT versus. ECA-MRI (95%CI):</u> J-1: CT: 0.74 (95%CI: 0.60-0.86) J-2: ECA-MRI: 0.81 (95%CI: 0.67-0.91) H-1: CT: 0.70 (95%CI: 0.50-0.86) H-2: ECA-MRI: 0.44 (95%CI: 0.27-0.62) G-1: CT: 0.71 (95%CI: 0.64-0.78) G-2: ECA-MRI: 0.81 (95%CI: 0.62-0.94)	

						D-1: CT: 0.59 (95%CI: 0.49-0.69) D-2: ECA-MRI: 0.72 (95%CI: 0.65-0. 79) C-1: CT: 0.53 (95%CI: 0.35-0.70) C-2: ECA-MRI: 0.67 (95%CI: 0.53-0.79) A-1: CT: 0.60 (95%CI: 0.47-0.72) A-2: ECA-MRI: 0.60 (95%CI: 0.50-0.69) I-1: CT: 0.44 (95%CI: 0.27-0.62) I-2: ECA-MRI: 0.62 (95%CI: 0.44-0.78) F-1: CT: 0.52 (95%CI: 0.38-0.66) F-2: ECA-MRI: 0.83 (95%CI: 0.72-0.91) Pooled characteristic ('type of statistical analysis' e.g. bivariate analysis) per index test and cut-off point: **Index test-1 (cut-off= ..)** 0.60 (95% CI 0.53 to 0.67) Heterogeneity (reasons): 62.43% **Index test-2 (cut-off= ..)**	

						0.69 (95%CI: 0.60-0.76) Heterogeneity: 74.74% <u>Specificity HCC<2cm CT versus. ECA-MRI (95%CI):</u> (e.g. sensitivity / specificity (%)) J-1: CT: 0.62-0.94 (95%CI: 0.62-0.94) J-2: ECA-MRI: 0.66-0.96 (95%CI: 0.66-0.96) H-1: CT: 0.70-1.00 (95%CI: 0.70-1.00) H-2: ECA-MRI: 0.84-1.00 (95%CI: 0.84-1.00) G-1: CT: 0.65-0.80 (95%CI: 0.65-0.80) G-2: ECA-MRI: 0.70-1.00 (95%CI: 0.70-1.00) D-1: CT: 0.74-0.93 (95%CI: 0.74-0.93) D-2: ECA-MRI: 0.78-0.90 (95%CI: 0.78-0.90) C-1: CT: 0.92-1.00 (95%CI: 0.92-1.00) C-2: ECA-MRI: 0.88-1.00 (95%CI: 0.88-1.00)	

						A-1: CT: 0.49-0.83 (95%CI: 0.49-0.83) A-2: ECA-MRI: 0.76-0.94 (95%CI: 0.76-0.94) I-1: CT: 0.84-1.00 (95%CI: 0.84-1.00) I-2: ECA-MRI: 0.95-1.00 (95%CI: 0.95-1.00) F-1: CT: 0.88-1.00 (95%CI: 0.88-1.00) F-2: ECA-MRI: 0.14-0.48 (95%CI: 0.14-0.48) Pooled characteristic ('type of statistical analysis' e.g. bivariate analysis) per index test and cut-off point: **Index test-1 (cut-off= ..)** 0.92 (95% CI 0.79 to 0.97) Heterogeneity (reasons): 82.42% **Index test-2 (cut-off= ..)** 0.94 (95%CI: 0.73-0.99 <u>Sensitivity HCC>2cm CT</u>	

						<u>versus. ECA-MRI (95%CI):</u> F-1: CT: 0.73 (95%CI: 0.61-0.83) F-2: ECA-MRI: 0.82 (95%CI: 0.63-0.94) D-1: CT: 0.93 (95%CI: 0.83-0.98) D-2: ECA-MRI: 0.96 (95%CI: 0.88-0.99) H-1: CT: 0.82 (95%CI: 0.63-0.94) H-2: ECA-MRI: 0.95 (95%CI: 0.86-0.99) G-1: CT: 0.72 (95%CI: 0.64-0.79) G-2: ECA-MRI: 0.73 (95%CI: 0.65-0.80) A-1: CT: 0.68 (95%CI: 0.45-0.86) A-2: ECA-MRI: 0.86 (95%CI: 0.65-0.97) Pooled characteristic ('type of statistical analysis' e.g. bivariate analysis) per index test and cut-off point: **Index test-1 (cut-off= ..)** 0.79 (95% CI 0.68 to 0.86) Heterogeneity (reasons): 70.44	

						Index test-2 (cut-off= ..) 0.89 (95%CI: 0.78-0.95) Heterogeneity: 88.31% <u>Specificity HCC>2cm CT versus. ECA-MRI (95%CI):</u> F-1: CT: 0.52-1.00 (95%CI: 0.52-1.00) F-2: ECA-MRI: 0.40-1.00 (95%CI: 0.40-1.00) D-1: CT: 0.73-0.98 (95%CI: 0.73-0.98) D-2: ECA-MRI: 0.52-1.00 (95%CI: 0.52-1.00) H-1: CT: 0.19-0.99 (95%CI: 0.19-0.99) H-2: ECA-MRI: 0.69-0.96 (95%CI: 0.69-0.96) G-1: CT: 0.81-0.99 (95%CI: 0.81-0.99) G-2: ECA-MRI: 0.89-1.00 (95%CI: 0.89-1.00) A-1: CT: 0.48-1.00 (95%CI: 0.48-1.00) A-2: ECA-MRI: 0.28-0.99 (95%CI: 0.28-0.99)	

						Pooled characteristic ('type of statistical analysis' e.g. bivariate analysis) per index test and cut-off point: **Index test-1 (cut-off= ..)** 0.92 (95% CI 0.83 to 0.96) Heterogeneity (reasons): 0% **Index test-2 (cut-off= ..)** 0.93 (95%CI: 0.82-0.97) Heterogeneity: 46.96% <u>Overall AUC (95%CI):</u> CT: 0.80 (0.76-0.83) ECA-MRI: 0.88 (0.85-0.91) <u>HCC<2cm AUC (95%CI:</u> CT: 0.72 (o.68-0.76) ECA-MRI: 0.79 (0.76-0.83) <u>HCC>2cm AUC (95%CI):</u>	

						CT: 0.93 (0.91-0.95) ECA-MRI: 0.96 (0.94-0.98)	
Li 2019 PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis *Literature search up to 08-01-2019* **A:** Kim 2009 **B**: Di Martino 2010 **C**: Akai 2011 **D**: Granito 2013 **E**: Maiwald 2014 **F**: Tsurusaki 2016 **G**: Imai 2017 **H**: Yoon 2019 <u>Study design</u>: all prospective <u>Setting and Country</u>: **A: Korea** **B**: Italy **C**: Japan **D**: Italy **E**: Germany **F**: Japan **G**: Ikeda **H**: Korea <u>Source of funding and conflicts of interest:</u>	Inclusion criteria SR: Article investigated accuracy of Gd-EOB-DTPA-MRI and MDCT for HCC, reference standard was pathological proof from liver explant / resection / biopsy, original data to calculate 2x2 table, prospective research, article in English Exclusion criteria SR: letters, systemic evaluations, review literature, comments, animal models, patient received only an MRI or CT, conference abstracts, non-English Only most detailed or most recent publication was included when encountering multiple reports. *8 studies included* <u>Important patient characteristics</u>: <u>N (number of lesions)</u> **A:** 62 (132) **B**: 58 (109) **C**: 34 (97) **D**: 33 (48)	Describe index and comparator tests* and cut-off point(s): A-1: CT 16/40/64, criteria: Ar A-2: MRI 3.0T, criteria: Ar B-1: CT 64, criteria: LI-RADS 4 + 5 B-2: MRI 1.5T, criteria: LI-RADS 4 + 5 C-1: CT 64, criteria: LI-RADS 4 + 5 C-2: MRI 1.5T, criteria: LI-RADS 4 + 5 D-1: CT 16, criteria: Ar D-2: MRI 1.5T, criteria: Ar E-1: CT 64, criteria: LI-RADS 4 + 5 E-2: MRI 3.0T, criteria: LI-RADS 4 + 5 F-1: CT 64, criteria: Any 2* F-2: MRI 3.0T, criteria: Any 2* G-1: CT 64, criteria: Ar G-2: MRI 1.5/3.0T, criteria: Ar H-1: CT 64, criteria: Ar H-2: MRI 1.5/3.0T, criteria: Ar *Any 2: any two positive criteria from:	Describe reference test and cut-off point(s): **A:** Pathology on explant **B**: Pathology on explant/biopsy or imaging follow-up **C**: Pathology on explant **D**: Pathology on explant or imaging follow-up **E**: Pathology on explant/biopsy or imaging follow-up **F**: Pathology on explant or imaging follow-up **G**: Pathology on explant or imaging follow-up **H**: Pathology on explant/biopsy Prevalence, calculated from number of lesions (%) (based on refence test at specified cut-off point)	Endpoint of follow-up: **A** >6 months **B**: 220 days (90-370) **C**: >6 months **D**: 24 months (22-28) **E**: 6 months **F**: 12 months (12-31) **G**: 385 days (86-1141) **H**: >6 months	Outcome measures and effect size (include 95%CI and p-value if available): <u>Overall sensitivity, CT versus MRI:</u> **Index test-1: CT (cut-off= ..)** 0.68 (95% CI 0.51-0.81) Heterogeneity (reasons): NA **Index test-2: MRI (cut-off= ..)** 0.85 (95%CI: 0.77-0.90) Heterogeneity (reasons): NA <u>Overall specificity, CT versus MRI:</u> **Index test-1: CT (cut-off= ..)** 0.92 (0.84-0.96) Heterogeneity (reasons): NA **Index test-2: MRI (cut-off= ..)** 0.94 (95%CI: 0.88-0.97)	**Accuracy on a per lesion base** <u>Study quality (ROB):</u> quadas-2; Di martino, Granito, Imai could be at high risk. Overall probably no high risk of bias.

	(commercial / non-commercial funding/ industrial co-authorship / potential conflicts of interest)	**E**: 50 (71) **F**: 54 (125) **G**: 97 (66) **H**: 131 (80) *Size, cm:* A: 2.9 (0.5–10.5) B: 1.8 (0.3–7.0) C: 2.6 (0.4–15.2) D: 1.8 (1.0–3.0) E: 3.3 F: 2.7 (0.5–14) G: 0.9 (0.5–2.0) H: < 2 cm (n = 124); > 2 cm (n = 7) *Sex, n males:* **A: 57** **B**: 39 **C**: 27 **D**: 58 **E**: 42 **F**: 39 **G**: 64 **H**: 85 Time between CT and MRI: **A:** <4 weeks **B**: >4 weeks **C**: >2 weeks **D**: >1 week **E**: >1 week **F**: <4 weeks **G**: 2.2 days (0-30) **H**: 13 days (0-30)	• Clearly visible hyperenhancement in arterial phase • Hypoattenuation or hypointensity compared to surrounding in portal venous or equilibrium phase • Peripheral rim enhancement in equilibrium • Infiltration of adjacent vessels • Hypointensity in delayed hepatobiliary phase	**A:** 62.9% **B**: 79.8% **C**: 53.6% **D**: 79.2% **E**: 100% **F**: 66.4% **G**: 100% **H**: 61.1% For how many participants were no complete outcome data available? N (%) NA Reasons for incomplete outcome data described? NA		Heterogeneity (reasons): NA ___ Sensitivity HCC<2cm, CT versus MRI: **Index test-1: CT (cut-off= ..)** 0.46 (95%CI: 0.32-0.61) Heterogeneity (reasons): NA **Index test-2: MRI (cut-off= ..)** 0.79 (95%CI: 0.67-0.87) Heterogeneity (reasons): NA Specificity HCC<2cm, CT versus MRI: **Index test-1: CT (cut-off= ..)** 0.93 (95%CI: 0.83-0.97) Heterogeneity (reasons): NA **Index test-2: MRI (cut-off= ..)** 0.92 (0.77-0.97) Heterogeneity (reasons): NA ___	

						<u>Sensitivity HCC>2cm, CT(1) versus MRI(2):</u> **B1:** 0.82 (0.67-0.93) **B2:** 0.84 (0.67-0.95 **D1:** 0.65 (0.38-0.86) **D2:** 0.82 (0.57-0.96) **H1:** 0.00 (0.00-0.52) **H2:** 0.00 (0.00-0.52) <u>Specificity HCC>2cm, CT(1) versus MRI(2):</u> **B1:** 0.00 (0.00-0.84) **B2:** 1.00 (0.29-1.00) **D1:** 1.00 (0.16-1.00) **D2:** 1.00 (0.16-1.00) **H1:** 1.00 (0.92-1.00) **H2:** 1.00 (0.16-1.00) ___ <u>Overall AUC (95%CI):</u> CT: 0.91 (0.88-0.93)	

						MRI: 0.96 (0.94-0.97) <u>HCC<2CM AUC (95%CI):</u> CT: 0.82 (0.78-0.85) MRI: 0.90 (0.87-0.93) AUC HCC>2cm not reported.	
Roberts 2018 PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis *Literature search up to 27-04-2016* **Contrast enhanced CT versus Gadoxetate-enhanced MRI** **A**: Xing 2010 **B**: Sun 2010 **C**: Sano 2011 **D**: Maiwald 2014 **E**: Kasai 2012 **F**: Hideka 2013 **G**: Haradome 2011 **H**: Chen 2016 **Contrast enhanced CT versus Extracellular contrast enhanced MRI**	Inclusion criteria SR: adults with cirrhosis and suspected HHC, diagnosis and staging of HCC with CE multiphasic CT compared to MRI with and without excracellular contrast or gadoxetate disodium, accuracy outcomes Exclusion criteria SR: non comparative studies, reviews, case reports, <5 patients in sample *33 studies included (n=8 for CT versus gadoxetate MRI; n=11 for CT versus extracellular agent MRI))* <u>Important patient characteristics</u>: *Number of patients; characteristics important to*	Describe index and comparator tests* and cut-off point(s): **Contrast enhanced CT versus Gadoxetate-enhanced MRI** A-1: triphasic CT A-2: mri with gadoxetate disodium B-1: CT 8 / 16 / 64 B-2: mri with gadoxetate disodium C-1: CT 16 C-2: mri with gadoxetate disodium D-1: CT 64 D-2: mri with Gd-EOB-DTPA E-1: Dynamic CT E-2: mri with Gd-EOB-DTPA F-1: MDCT 64 F-2: mri with Gd-EOB-DTPA G-1: MDCT 16 G-2: mri with Gd-EOB-DTPA	Describe reference test and cut-off point(s): A: NR B: histopathology or imaging and lab findings C: pathology D: biopsy E: All available clinical findings (incl: imaging, lab, histopathology and follow-up) F: histopathology G: pathology in resection or finen eedle biopsy H: pathology or imaging follow-up I: histology or angiographic	Endpoint of follow-up: NR	Outcome measures and effect size (include 95%CI and p-value if available): <u>Sensitivity CECT (1) versus MRI with and without contrast (2), 19 studies:</u> **Index test-1 (CT)** 0.66 (95% CI 0.60 to 0.72) Heterogeneity (reasons): 72.53% **Index test-2 (MRI)** 0.82 (95%CI: 0.75-0.87) Heterogeneity: 72.90% <u>Specificity CECT (1) versus MRI with</u>	Overlap with Chen 2022 for extracellular: • Golfieri • Hassan • Khalli • Di Martino • Leoni • Sangiovanni • Serste Included in Chen 2022, not in Roberts 2018 for extracellular: • Basha (high risk of bias: unclear index test, unclear ref std, high risk patient flow) • Min (low risk: unclear for index test, other domains low) • Ronot (high risk: high risk patient flow,

	I: Ueda 1996 J: Serste 2012 K: Sangiovanni 2010 L: Rode 2001 M: Puig 1997 N: Libbrecht 2002 O: Leoni 2010 P: Khalli 2011 Q: Hassan 2011 R: Golfieri 2009 S: Di Martino 2013 <u>Study design</u>: A: Prospective B: NR C: retrospective D: Prospective E: retrospective F: retrospective G: retrospective H: retrospective I: retrospective J: case-only observational K: prospective L: Prospective M: NR N: Retrospective O: NR P: Retrospective Q: retrospective R: prospective S: Prospective	*the research question; for example, age, sex, bmi, ...* <u>N:</u> A: 39 B: 69 C: 64 D: 50 E: 47 F: 11 G: 75 H: 139 I: 512 J: 74 K: 64 L: 43 M: 50 N: 49 O: 60 P: 84 Q: 61 R: 63 S: 140 <u>*Sex (n male)*</u>*:* A: NR B: 56 C: 47 D: 42 E: 35 F: NR G: 60 H: 101 I: 385 J: 58 K: 47 L: 30	H-1: Dynamic CT H-2: mri with Gadoxetate disodium **Contrast enhanced CT versus Extracellular contrast enhanced MRI** I-1: CT I-2: mri (NR) J-1: MDCT J-2: mri (NR) K-1: MDCT 64 K-2: mri with gadolinium L-1: CT 64 L-2: mri with gadolinium M-1: MDCT M-2: mri with dgadolinium N-1: Dynamic CT N-2: mri with dimeglumine gadopentetate or maglumine gadoterate O-1: quadruple phase MDCT O-2: mri with supramagnetic iron oxide and gadolinium P-1: MDCT 64 P-2: mri with gadobenate diglumine Q-1: triphasic MDCT Q-2: mri with gadodiamide R-1: quadruple phase MDCT R-2: mri with gadopentetate dimeglumine S-1: CT 64	findings and follow-up J: biopsy K: biopsy L: pathology M: NR N: biopsy O: biopsy P: biopsy, imaging or follow-up Q: biopsy or clinical and radiological follow-up R: pathology on transplant / resection / biopsy or follow-up S: pathology or follow-up Prevalence (%) (based on refence test at specified cut-off point) NR For how many participants were no complete		<u>and without contrast (2), 19 studies:</u> **Index test-1 (CT)** 0.92 (95% CI 0.84 to 0.96) Heterogeneity (reasons): 86.74% **Index test-2 (MRI)** 0.91 (95%CI: 0.82-0.95) Heterogeneity: 89.81% ___ <u>Sensitivity CECT (1) versus gadoxetate enhanced MRI (2):</u> A-1: 0.81 (0.69-0.90) A-2: 0.86 (0.75-0.94) B-1: 0.55 (0.36-0.72) B-2: 0.91 (0.76-0.98) C-1: 0.64 (0.53-0.74) C-2: 0.96 (0.89-0.99) D-1: 0.85 (0.65-0.96) D-2: 0.92 (0.75-0.99) E-1: 0.74 (0.61-0.85)	other domains unclear) Included in Roberts 2018, not in Chen 2022 for extracellular: • Ueda (high risk of bias) • Puig (low/unclear risk of bias) • Libbrecht (high for patient selection, unclear for index test, low for ref std and patient flow) • Rode (low risk) <u>Study quality (ROB):</u> QUADAS-2 by authors: **Contrast enhanced CT versus Gadoxetate-enhanced MRI** 4/8 studies high risk for patient selection bias and 1/8 unclear. Low risk of bias on other domains. **Contrast enhanced CT versus Extracellular contrast enhanced MRI** 5/11 studies have high risk of bias on both the reference standard and patient flow; 2 studies unclear on both

	Setting and Country: A: China B: South Korea C: Japan D: Germany E: Japan F: Japan G: NR H: Japan I: Japan J: France K: Italy L: France M: Italy N: Belgium O: Italy P: Canada Q: Kuwait R: italy S: Italy Source of funding and conflicts of interest: One author consults for Bayer and is on the speakers' bureau; this author also received grants from GE and Siemens.	M: NR N: 32 O: 52 P: 53 Q: 37 R: 53 S: 104 Age: A: NR B: 55.8 (39-73) C: 67±9.3 D: 60.6 (29-84) E: 65.4±9.1 F: NR G: 54.7 (42-67) H: 68 ± 11 I: 54.6 J: 60 (38-88) K: 65 (44-80) L: 51 (27-65) M: NR N: 53.4±11.6 O: 65.2±10 P: 58 (22-79) Q: 46.5 (19-74 R: 63.3 S: 66 (23-82) N lesions: A: NR B: 97 C: 108 D: NR E: 112 F: 17 G: 86	S-2: mri with gadobenate diglumine	outcome data available? NR		E-2: 0.93 (0.83-0.98) F-1: 0.56 (0.35-0.75) F-2: 0.59 (0.39-0.78) G-1: 0.70 (0.57-0.81) G-2: 0.77 (0.64-0.87) H-1: 0.87 (0.80-0.93) H-2: 0.86 (0.78-0.92) **Index test-1 (CT)** 0.73 (95% CI 0.64 to 0.81) Heterogeneity (reasons): 76.35% **Index test-2 (MRI)** 0.87 (95%CI: 0.79-0.93) Heterogeneity: 78.12% Specificity CECT (1) versus gadoxetate enhanced MRI (2): A-1: 0.92 (0.81-0.98) A-2: 0.94 (0.85-0.99) B-1: 0.98 (0.81-1.00) B-2: 0.93 (0.76-0.99	domains. 3/11 studies have high risk of bias on patient selection, 1 study unclear.

		H: 139 I: 61 J: 56 K: 67 L: 59 M: 83 N: 130 O: 75 P: 101 Q: 95 R: 123 S: 254 <u>Tumor size</u> A: NR B: 1.37±0.41 C: 0.4-2 D: NR E: NR F: <3 G: 1.74 ±0.6 H: 0.05-3 I: NR J: 1 to 2 K: <1cm: 2 / 1-2cm: 55 / >2cm: 2 L: 1.24 M: NR N: 27.5±10.6 (CT) / 26.0±11.5 (MRI) O: 1.8 (1-3) P: 1 to 2 Q: NR R: 1 to 3 S: NR				C-1: 0.98 (0.95-1.00) C-2: 0.96 (0.91-0.98) D-1: 0.75 (0.53-0.90) D-2: 0.75 (0.53-0.90) E-1: 1.00 (0.94-1.00) E-2: 0.98 (0.91-1.00) F-1: 0.88 (0.64-0.99) F-2: 0.94 (0.71-1.00) G-1: 0.95 (0.83-0.99) G-2: 0.95 (0.83-0.99) H-1: 1.00 (0.88-1.00) H-2: 0.96 (0.82-1.00) **Index test-1 (CT)** 0.96 (95% CI 0.90 to 0.98) Heterogeneity (reasons): 80.31% **Index test-2 (MRI)** 0.94 (95%CI: 0.90-0.97) Heterogeneity: 60.07% ___	

						<u>Sensitivity CECT (1) versus extracellular agent MRI (2):</u> I-1: 0.60 (0.44-0.75) I-2: 0.72 (0.52-0.85) J-1: 0.79 (0.64-0.89) J-2: 0.94 (0.82-0.99) K-1: 0.44 (0.27-0.62) K-2: 0.44 (0.27-0.62) L-1: 0.54 (0.25-0.81) L-2: 0.77 (0.46-0.95) M-1: 0.48 (0.36-0.61) M-2: 0.74 (0.62-0.84) N-1: 0.50 (0.01-0.99) N-2: 0.70 (0.35-0.93) O-1: 0.64 (0.50-0.76) O-2: 0.75 (0.61-0.85) P-1: 0.53 (0.35-0.70) P-2: 0.62 (0.44-0.78)	

						Q-1: 0.62 (0.42-0.79) Q-2: 0.90 (0.74-0.98) R-1: 0.62 (0.51-0.72) R-2: 0.84 (0.74-0.91) S-1: 0.72 (0.64-0.79) S-2: 0.72 (0.64-0.79) **Index test-1 (CT)** 0.61 (95% CI 0.54 to 0.87) Heterogeneity (reasons): 57.77% **Index test-2 (MRI)** 0.75 (0.67-0.82) Heterogeneity: 73.67% <u>Specificity CECT (1) versus extracellular agent MRI (2):</u> I-1: 0.85 (0.62-0.97) I-2: 0.75 (0.51-0.91) J-1: 0.48 (0.29-0.68) J-2: 0.52 (0.32-0.71) K-1: 1.00 (0.84-1.00)	

						K-2: 1.00 (0.84-1.00) L-1: 0.93 (0.83-0.98) L-2: 0.57 (0.43-0.70) M-1: 0.29 (0.04-0.71) M-2: 0.86 (0.42-1.00) N-1: 0.79 (0.49-0.95) N-2: 0.82 (0.57-0.96) O-1: 0.95 (0.75-1.00) O-2: 0.95 (0.75-1.00) P-1: 0.99 (0.92-1.00) P-2: 1.00 (0.95-1.00) Q-1: 0.83 (0.72-0.91) Q-2: 0.88 (0.77-0.94) R-1: 0.72 (0.55-0.80) R-2: 0.36 (0.21-0.54) S-1: 0.87 (0.78-0.93) S-2: 0.87 (0.78-0.93) Pooled characteristic ('type of statistical	

						analysis' e.g. bivariate analysis) per index test and cut-off point: **Index test-1 (CT)** 0.87 (95% CI 0.73 to 0.94) Heterogeneity (reasons): 84.84% **Index test-2 (MRI)** 0.86 (0.68-0.95) Heterogeneity: 90.04% ___ <u>Lesion <2cm, CECT (1) versus gadoxetate MRI (2) (2 studies), sensitivity:</u> **Index test-1 (CT)** 0.68 (0.55-0.79) Heterogeneity (reasons): 23.2% **Index test-2 (MRI)** 0.76 (0.67-0.84) Heterogeneity: 0% <u>Lesion <2cm, CECT (1) versus gadoxetate MRI (2) (2 studies), specificity:</u> **Index test-1 (CT)** 0.98 (0.90-1.00)	

						Heterogeneity (reasons): 13.3% **Index test-2 (MRI)** 0.96(0.87-0.99) Heterogeneity: 0% ___ <u>Lesion <1cm, CECT (1) versus extracellular MRI (2) (2 studies), sensitivity:</u> **Index test-1 (CT)** 0.48 (0.32-0.62) Heterogeneity (reasons): 52% **Index test-2 (MRI)** 0.69 (0.54-0.81) Heterogeneity: 94.6% <u>Lesion <1cm, CECT (1) versus extracellular MRI (2) (2 studies), specificity:</u> **Index test-1 (CT)** 0.69 (0.51-0.83) Heterogeneity (reasons): 0% **Index test-2 (MRI)** 0.46 (0.29-0.63) Heterogeneity: 84.3% ___	

						<u>Lesion >2cm, CECT (1) versus extracellular MRI (2) (3 studies), sensitivity:</u> **Index test-1 (CT)** 0.79 (0.70-0.86) Heterogeneity (reasons): 88.2% **Index test-2 (MRI)** 0.88 (0.80-0.93) Heterogeneity: 70.5% <u>Lesion >2cm, CECT (1) versus extracellular MRI (2) (3 studies), specificity:</u> **Index test-1 (CT)** 0.90 (0.76-0.97) Heterogeneity (reasons): 0% **Index test-2 (MRI)** 0.87 (0.73-0.96) Heterogeneity: 0% —— <u>Lesion 1-2cm, CECT (1) versus extracellular MRI (2) (6 studies), sensitivity:</u> **Index test-1 (CT)** 0.64 (0.58-0.70)	

						Heterogeneity (reasons): 61.79% **Index test-2 (MRI)** 0.70 (0.64-0.75) Heterogeneity: 80.4% <u>Lesion 1-2cm, CECT (1) versus extracellular MRI (2) (6 studies), specificity:</u> **Index test-1 (CT)** 0.88 (0.82-0.92 Heterogeneity (reasons): 90.89% **Index test-2 (MRI)** 0.87 (0.81-0.91) Heterogeneity: 92.1%	

Table of quality assessment for systematic reviews of diagnostic 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**	**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**
Chen 2022	No Reason: not reported, but the PICO elements can be	Yes Reason: date and strategy described and searched in	No Reason: includes studies are described. Reasons are provided for	Yes Reason: Described in tables 1 and 2.	Yes Reason: QUADAS-2 was used.	Unclear Reason: heterogeneity is observed in the meta-analyses. Different procedures were used for	Yes Reason: assessed	No Reason: not for the included 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	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
	deduced from the inclusion criteria	multiple databases.	excluded studies, but not referenced.			CT and MRI between studies, however it is unclear whether this could explain the variability.		
Li 2019	Yes Reason: aim was provided but could have included more PICO elements. PICO elements are deducible from the inclusion criteria	Yes Reason: date and strategy described and searched in multiple databases.	No Reason: includes studies are described. Reasons are not provided for excluded studies and are not referenced.	Yes Reason: Described in tables 2 and 3.	Yes Reason: QUADAS-2 was used.	Unclear Reasons: Unclear whether different characteristics explain the heterogeneity observed.	Yes Reason: assessed	No Reason: not for the included studies
Roberts 2018	Yes Reason: PICO provided	Yes Reason: date and strategy described and searched in multiple databases.	No Reason: includes studies are described. Reasons are provided for excluded studies, but not referenced.	Yes Reason: Described in tables 2.	Yes Reason: QUADAS-2 was used.	Unclear Reason: heterogeneity is observed in the meta-analyses. Unclear whether different characteristics explain the heterogeneity.	Yes Reason: assessed	No Reason: not for the included studies

Table of quality assessment for systematic reviews of diagnostic 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:

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
Chen 2022	No Reason: not reported, but the PICO elements can be deduced from the inclusion criteria	Yes Reason: date and strategy described and searched in multiple databases.	No Reason: includes studies are described. Reasons are provided for excluded studies, but not referenced.	Yes Reason: Described in tables 1 and 2.	Yes Reason: QUADAS-2 was used.	Unclear Reason: heterogeneity is observed in the meta-analyses. Different procedures were used for CT and MRI between studies, however it is unclear whether this could explain the variability.	Yes Reason: assessed	No Reason: not for the included studies
Li 2019	Yes Reason: aim was provided but could have included more PICO elements. PICO elements are deducible from the inclusion criteria	Yes Reason: date and strategy described and searched in multiple databases.	No Reason: includes studies are described. Reasons are not provided for excluded studies and are not referenced.	Yes Reason: Described in tables 2 and 3.	Yes Reason: QUADAS-2 was used.	Unclear Reasons: Unclear whether different characteristics explain the heterogeneity observed.	Yes Reason: assessed	No Reason: not for the included studies
Roberts 2018	Yes Reason: PICO provided	Yes Reason: date and strategy described and searched in multiple databases.	No Reason: includes studies are described. Reasons are provided for excluded studies, but not referenced.	Yes Reason: Described in tables 2.	Yes Reason: QUADAS-2 was used.	Unclear Reason: heterogeneity is observed in the meta-analyses. Unclear whether different characteristics explain the heterogeneity.	Yes Reason: assessed	No Reason: not for the included studies

Table of excluded studies

Author and year	Reason for exclusion
Ahn, Y. and Choi, S. H. and Jang, J. K. and Kim, S. Y. and Shim, J. H. and Lee, S. S. and Byun, J. H. (2022), Impact of the Liver Imaging Reporting and Data System on Research Studies of Diagnosing Hepatocellular Carcinoma Using MRI	Does not seem to contain a head-to-head comparison
Asemota, J. (2017), Review of current trends in imaging and surgical management of hepatocellular carcinoma	Conference abstract
Asemota, Joseph and Saleh, Mohammed and Igbinovia, Osato and Burns, Danny (2020), A Concise Review on Current Trends in Imaging and Surgical Management of Hepatocellular Carcinoma	Narrative
Chen, L. and Zhang, L. and Bao, J. and Zhang, J. and Li, C. and Xia, Y. and Huang, X. and Wang, J. (2013), Comparison of MRI with liverspecific contrast agents and multidetector row CT for the detection of hepatocellular carcinoma: A meta-analysis of 15 direct comparative studies	Post script / letter to the editor
Chou, R. and Cuevas, C. and Fu, R. and Devine, B. and Wasson, N. and Ginsburg, A. and Zakher, B. and Pappas, M. and Graham, E. and Sullivan, S. D. (2015), Imaging techniques for the diagnosis of hepatocellular carcinoma: A systematic review and meta-analysis	Unclear which studies are used for the subanalyses
Chou, Roger and Cuevas, Carlos and Fu, Rongwei and Devine, Beth and Wasson, Ngoc and Ginsburg, Alexander and Zakher, Bernadette and Pappas, Miranda and Graham, Elaine and Sullivan, Sean (2014), Imaging Techniques for the Diagnosis and Staging of Hepatocellular Carcinoma	Seems to be surpassed by newer reviews (e.g. Roberts 2018, Chen 2022)
Colli, Agostino and Fraquelli, Mirella and Casazza, Giovanni and Massironi, Sara and Colucci, Alice and Conte, Dario and Duca, Piergiorgio (2006), Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review	Does not seem to contain a head-to-head comparison
Dondi, F. and Albano, D. and Cerudelli, E. and Gazzilli, M. and Giubbini, R. and Treglia, G. and Bertagna, F. (2020), Radiolabelled PSMA PET/CT or PET/MRI in hepatocellular carcinoma (HCC): a systematic review	Does not seem to contain a head-to-head comparison
Duncan, J. K. and Ma, N. and Vreugdenburg, T. D. and Cameron, A. L. and Maddern, G. (2017), Gadoxetic acid-enhanced MRI for the characterization of hepatocellular carcinoma: A systematic review and meta-analysis	Also includes patients with known HCC instead of suspected only
Fitzmorris, P. and Singal, A. K. (2015), Surveillance and diagnosis of hepatocellular carcinoma	Narrative
Floriani, I. and D'Onofrio, M. and Rulli, E. and Chen, M. H. and Li, R. and Musicco, L. (2013), Performance of imaging modalities in the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis	Also Includes patients with known HCC instead of suspected only
Gilhotra, R. and Htut, S. and McGowan, C. and Gururatsakul, M. and Peter-Kini, G. and Boyd, P. (2020), The importance of a multidisciplinary team in assessing Liver Imaging Reporting and Data System indeterminate lesions: Wait and watch or biopsy?	Conference/poster abstract
Guo, J. and Seo, Y. and Ren, S. and Hong, S. and Lee, D. and Kim, S. and Jiang, Y. (2016), Diagnostic performance of contrast-enhanced multidetector computed tomography and gadoxetic acid disodium-enhanced magnetic resonance imaging in detecting hepatocellular carcinoma: direct comparison and a meta-analysis	Also includes patients retrospectively diagnosed with HCC instead of suspected only
Hanna, R. F. and Miloushev, V. Z. and Tang, A. and Finklestone, L. A. and Brejt, S. Z. and Sandhu, R. S. and Santillan, C. S. and Wolfson, T. and Gamst, A. and Sirlin, C. B. (2016), Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma	Unclear whether there are individual primary studies with a direct head-to-head comparison
Jhaveri, K. and Cleary, S. and Audet, P. and Balaa, F. and Bhayana, D. and Burak, K. and Chang, S. and Dixon, E. and Haider, M. and Molinari, M. and Reinhold, C. and Sherman, M. (2015), Consensus statements from a multidisciplinary expert panel on the utilization and application of a liver-specific MRI Contrast agent (gadoxetic acid)	Consensus statements
Kang, Ji Hun and Choi, Sang Hyun and Lee, Ji Sung and Kim, Kyung Won and Kim, So Yeon and Lee, Seung Soo and Byun, Jae Ho (2021), Inter-reader reliability of CT Liver Imaging Reporting and Data System according to imaging analysis methodology: a systematic review and meta-analysis	Does not seem to contain a head-to-head comparison

Karmazanovsky, G. G. and Shantarevich, M. Yu (2021), The review of international clinical guidelines and clinical trial results for the diagnosis of hepatocellular cancer (HCC) for the period 2014-2020	Article in Russian
Kim, D. H. and Choi, S. H. and Park, S. H. and Kim, K. W. and Byun, J. H. and Kim, S. Y. and Lee, S. S. and Choi, J. I. (2021), The Liver Imaging Reporting and Data System tumor-in-vein category: a systematic review and meta-analysis	Does not seem to contain a head-to-head comparison
Kim, D. W. and Choi, S. H. and Lee, J. S. and Kim, S. Y. and Lee, S. J. and Byun, J. H. (2021), Interreader reliability of liver imaging reporting and data system treatment response: A systematic review and meta-analysis	Does not seem to contain a head-to-head comparison
Kim, Y. Y. and Lee, S. and Shin, J. and Son, W. J. and Shin, H. and Lee, J. E. and Hwang, J. A. and Chung, Y. E. and Choi, J. Y. and Park, M. S. (2021), Diagnostic Performance of Liver Imaging Reporting and Data System Version 2017 Versus Version 2018 for Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis of Comparative Studies	Does not seem to contain a head-to-head comparison
Lee, S. and Kim, S. S. and Roh, Y. H. and Choi, J. Y. and Park, M. S. and Kim, M. J. (2020), Diagnostic Performance of CT/MRI Liver Imaging Reporting and Data System v2017 for Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis	Does not seem to contain a head-to-head comparison
Lee, S. and Kim, Y. Y. and Shin, J. and Hwang, S. H. and Roh, Y. H. and Chung, Y. E. and Choi, J. Y. (2020), CT and MRI Liver Imaging Reporting and Data System Version 2018 for Hepatocellular Carcinoma: A Systematic Review With Meta-Analysis	Does not seem to contain a head-to-head comparison
Lee, Y. J. and Lee, J. M. and Lee, J. S. and Lee, H. Y. and Park, B. H. and Kim, Y. H. and Han, J. K. and Choi, B. I. (2015), Hepatocellular carcinoma: Diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis	Unclear which studies are used for the analyses
Lei, J. and Wang, Y. and Li, Z. and Guo, S. and Wang, X. and Zhai, Y. and Yang, K. (2014), Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging for the detection of hepatocellular carcinoma: A meta-analysis	Does not seem to contain a head-to-head comparison
Li, L. and Hu, Y. and Han, J. and Li, Q. and Peng, C. and Zhou, J. (2021), Clinical application of liver imaging reporting and data system for characterizing liver neoplasms: A meta-analysis	Does not seem to contain a head-to-head comparison
Liang, Y. and Xu, F. and Guo, Y. and Lai, L. and Jiang, X. and Wei, X. and Wu, H. and Wang, J. (2021), Diagnostic performance of LI-RADS for MRI and CT detection of HCC: A systematic review and diagnostic meta-analysis	Does not seem to contain a head-to-head comparison
Liu, X. and Jiang, H. and Chen, J. and Zhou, Y. and Huang, Z. and Song, B. (2017), Gadoxetic acid disodium,Äìenhanced magnetic resonance imaging outperformed multidetector computed tomography in diagnosing small hepatocellular carcinoma: A meta-analysis	Includes studies using imaging as a reference standard (not in radiological follow-up)
Nadarevic, T. and Colli, A. and Giljaca, V. and Fraquelli, M. and Casazza, G. and Manzotti, C. and ≈†timac, D. and Miletic, D. (2022), Magnetic resonance imaging for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease	Does not seem to contain a head-to-head comparison
Nadarevic, T. and Giljaca, V. and Colli, A. and Fraquelli, M. and Casazza, G. and Miletic, D. and ≈†timac, D. (2021), Computed tomography for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease	Does not seem to contain a head-to-head comparison
Park, E. J. and Son, J. H. and Choi, S. H. (2022), Imaging features of hepatocellular carcinoma in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: a systematic review and meta-analysis	Does not seem to contain a head-to-head comparison
Tang, A. and Bashir, M. R. and Corwin, M. T. and Cruite, I. and Dietrich, C. F. and Do, R. K. G. and Ehman, E. C. and Fowler, K. J. and Hussain, H. K. and Jha, R. C. and Karam, A. R. and Mamidipalli, A. and Marks, R. M. and Mitchell, D. G. and Morgan, T. A. and Ohliger, M. A. and Shah, A. and Vu, K. N. and Sirlin, C. B. (2018), Evidence supporting LI-RADS major features for CT- and MR imaging-based diagnosis of hepatocellular carcinoma: A systematic review	Narrative
Tang, E. S. T. and Hall, G. and Yu, D. and Menard, A. and Hopman, W. and Nanji, S. (2019), Predictors and Cumulative Frequency of Hepatocellular Carcinoma in High and Intermediate LI-RADS Lesions: A Cohort Study from a Canadian Academic Institution	Does not seem to contain a head-to-head comparison
Usman, S. and Smith, L. and Brown, N. and Major, V. (2018), Diagnostic accuracy of Magnetic Resonance Imaging using liver tissue specific contrast	No meta-analysis of studies

agents and contrast enhanced Multi Detector Computed Tomography: A systematic review of diagnostic test in Hepatocellular Carcinoma (HCC)	
van der Pol, C. B. and Lim, C. S. and Sirlin, C. B. and McGrath, T. A. and Salameh, J. P. and Bashir, M. R. and Tang, A. and Singal, A. G. and Costa, A. F. and Fowler, K. and McInnes, M. D. F. (2019), Accuracy of the Liver Imaging Reporting and Data System in Computed Tomography and Magnetic Resonance Image Analysis of Hepatocellular Carcinoma or Overall Malignancy,ÃîA Systematic Review	Does not seem to contain a head-to-head comparison
van der Pol, C. B. and McInnes, M. D. F. and Salameh, J. P. and Chernyak, V. and Tang, A. and Bashir, M. R. (2022), Impact of Reference Standard on CT, MRI, and Contrast-enhanced US LI-RADS Diagnosis of Hepatocellular Carcinoma: A Meta-Analysis	Editorial
van der Pol, C. B. and McInnes, M. D. F. and Salameh, J. P. and Levis, B. and Chernyak, V. and Sirlin, C. B. and Bashir, M. R. and Allen, B. C. and Burke, L. M. B. and Choi, J. Y. and Choi, S. H. and Forner, A. and Fraum, T. J. and Giamperoli, A. and Jiang, H. and Joo, I. and Kang, Z. and Kierans, A. S. and Kang, H. J. and Khatri, G. and Kim, J. H. and Kim, M. J. and Kim, S. Y. and Kim, Y. Y. and Kwon, H. and Lee, J. M. and Lewis, S. C. and McGinty, K. A. and Mulazzani, L. and Park, M. S. and Piscaglia, F. and Podgv≥rska, J. and Reiner, C. S. and Ronot, M. and Rosiak, G. and Song, B. and Song, J. S. and Tang, A. and Terzi, E. and Wang, J. and Wang, W. and Wilson, S. R. and Yokoo, T. (2022), CT/MRI and CEUS LI-RADS Major Features Association with Hepatocellular Carcinoma: Individual Patient Data Meta-Analysis	Compares imaging features. Does not seem to contain a head-to-head comparison
Wu, L. M. and Xu, J. R. and Gu, H. Y. and Hua, J. and Chen, J. and Zhu, J. and Zhang, W. and Hu, J. (2013), Is liver-specific gadoxetic acid-enhanced magnetic resonance imaging a reliable tool for detection of hepatocellular carcinoma in patients with chronic liver disease?	Seems to be surpassed by newer reviews on gd-eob-dtpa (e.g. Roberts 2018, Li 2019)
Ye, F. and Liu, J. and Ouyang, H. and Lin, W. (2015), Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging and multidetector-row computed tomography for the diagnosis of hepatocellular carcinoma: A systematic review and meta-analysis	Overlap with Li 2019
Youn, S. Y. and Kim, D. H. and Choi, S. H. and Kim, B. and Choi, J. I. and Shin, Y. R. and Oh, S. N. and Rha, S. E. (2021), Diagnostic performance of Liver Imaging Reporting and Data System treatment response algorithm: a systematic review and meta-analysis	Does not seem to contain a head-to-head comparison
Zech, C. J. and Potthoff, A. and Ricke, J. (2018), Radiological imaging and response assessment in HCC	Narrative, article in German
Zhou, Yan and Qin, Zhengyi and Ding, Jianmin and Zhao, Lin and Chen, Ying and Wang, Fengmei and Jing, Xiang (2022), Risk Stratification and Distribution of Hepatocellular Carcinomas in CEUS and CT/MRI LI-RADS: A Meta-Analysis	Does not seem to contain a head-to-head comparison

Literature search strategy

Algemene informatie

Richtlijn: NVMDL Hepatocellulair carcinoom (HCC)	
Uitgangsvraag: Welk onderzoek is het beste voor de diagnose van HCC.?	
Database(s): Ovid/Medline, Embase	Datum: 23-6-2022
Periode: nvt	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: HCC EN MRI EN CT EN sensitivity, specificity Vanwege de hoge aantallen wordt gestart met de SRs. Alle sleutelartikelen worden gevonden.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 23-6-2022 met relevante zoektermen gezocht naar systematische reviews over MRI en CT voor de diagnose hepatocellulair carcinoom. De literatuurzoekactie leverde 113 unieke treffers op.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	105	61	113
RCTs			
Observationele studies			
Overig			
Totaal			113

5

Zoekstrategie

Embase

No.	Query	Results
#16	#6 AND #15	6
#15	#9 OR #10 OR #11 OR #12 OR #13 OR #14	6
#14	enhanced AND mri AND with AND 'diffusion weighted' AND imaging AND superior AND to AND '64 slice' AND 'contrast enhanced' AND ct AND for AND the AND diagnosis AND of AND hepatocellular AND carcinoma AND maiwald	1
#13	hepatocellular AND carcinoma AND in AND cirrhotic AND patients AND prospective AND comparison AND of AND us, AND ct AND mr AND imaging AND di AND martino AND 2013	1
#12	gadolinium AND ethoxybenzyl AND diethylenetriamine AND pentaacetic AND acid AND enhanced AND magnetic AND resonance AND imaging AND 'multidetector row' AND computed AND tomography AND for AND the AND diagnosis AND of AND hepatocellular AND carcinoma AND ye AND 2015	1
#11	diagnostic AND performance AND of AND 'contrast enhanced' AND multidetector AND computed AND tomography AND gadoxetic AND acid AND 'disodium enhanced' AND magnetic AND resonance AND imaging AND in AND detecting AND hepatocellular AND carcinoma AND guo	1
#10	computed AND tomography AND for AND the AND diagnosis AND of AND hepatocellular AND carcinoma AND in AND adults AND with AND chronic AND liver AND disease AND 2021 AND nadarevic NOT magnetic:ti NOT abdominal:ti	1
#9	hepatocellular AND carcinoma AND diagnostic AND performance AND of AND multidetector AND ct AND mr AND imaging AND lee AND 2015 NOT computed:ti	1
#8	#6 AND #7	105

#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	833621
#6	#4 AND #5	2485
#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	9233444
#4	#1 AND #2 AND #3	5035
#3	'computer assisted tomography'/exp OR 'cat scan':ti,ab,kw OR ((compute* NEAR/3 tomograph*):ti,ab,kw) OR ct:ti,ab,kw	1557930
#2	'nuclear magnetic resonance imaging'/exp/mj OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ab,ti OR fmris:ab,ti	1017169
#1	'liver cell carcinoma'/exp/mj OR ('liver cancer'/de AND 'primary tumor'/de) OR (((hepat* OR liver) NEAR/3 carcinom*):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw OR ((primary NEAR/3 liver):ti,ab,kw)	215358

Ovid/Medline

#	Searches	Results
8	6 and 7	61
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/))	572259
6	4 and 5	1739
5	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	7418284

	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/	
4	1 and 2 and 3	3434
3	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.	798060
2	exp magnetic resonance imaging/ or ("magnetic resonance" and (image or images or imaging)).ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or "mr tomography".ti,ab,kf. or "mr tomographies".ti,ab,kf. or "mr tomographic".ti,ab,kf. or "proton spin".ti,ab,kf. or ((magneti* or "chemical shift") and imaging).ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf.	894135
1	Carcinoma, Hepatocellular/ or (hepat* adj3 carcinom*).ti,ab,kf. or hepatocarcinom*.ti,ab,kf. or hepatoma.ti,ab,kf. or (liver adj3 primary).ti,ab,kf.	164763

Module 3 Biopt pro diagnosi

Uitgangsvraag

Wat is de rol van biopsie pro diagnosi om een hepatocellulair carcinoom te detecteren bij patiënten met of zonder levercirrose?

Inleiding

Niet-invasieve diagnostiek middels imaging (CT/MRI/CEUS) van hepatocellulair carcinoom bij bekende levercirrose heeft een relatief hoge specificiteit, zeker voor grotere tumoren. Voor kleinere laesies (< 2 cm) is beeldvormende diagnostiek in principe minder/ niet specifiek, evenals in de context van non-cirrose (waarbij ook alternatieve laesies moeten worden overwogen als bv hepatocellulair adenoom (HCA), hypervasculaire metastasen etc.). Het biopteren van kleinere laesies gaat echter gepaard met grotere kans op sampling error, omdat laesies moeilijker zijn aan te prikken, waardoor weefsel vaker niet representatief is.

Daarom wordt bij deze zoekvraag voor het stellen van de diagnose hepatocellulair carcinoom uitgegaan van een 'gouden standaard' op basis van klinische follow-up en/of een resectiepreparaat.

Search and select

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

What is the diagnostic accuracy of a biopsy pro diagnosi compared to imaging modalities (MRI or CT) to detect a hepatocellular carcinoma in patients with or without cirrhosis/liver disease, with pathology on resected material (for resectable patients) or a clinical follow-up (for unresectable lesions) as a reference?

P: patients suspected of a hepatocellular carcinoma with or without cirrhosis or liver disease;
I: biopsy of the tumor/lesion (to detect a hepatocellular carcinoma pro diagnosi)
C: imaging with MRI or CT;
R: pathological assessment on resected material (for lesions which are resectable) or clinical follow-up (for lesions who are non resectable);
O: sensitivity, specificity, positive predictive value, negative predictive value, area under the curve.

<u>Relevant outcome measures</u>

The guideline development group considered unequivocal diagnosis of hepatocellular carcinoma (HCC) as a critical outcome measure for decision making; and suspicion of HCC 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.

<u>Search and select (Methods)</u>

The databases Medline (via OVID) and Embase (via Embase.com) were searched for systematic reviews with relevant search terms until 27 June 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 199 hits. Studies were selected based on the following criteria: patients were suspected of having a hepatocellular carcinoma (with or without cirrhosis or liver disease), biopsy was used as an index test to diagnose a hepatocellular carcinoma, biopsy was compared with a imaging (MRI or CT) as a comparator test, pathology on resected material (for resectable

lesions) or a clinical follow-up (for unresectable lesions) was used as a reference standard, and at least one outcome of interest was reported or could be calculated from the presented data. Forty systematic reviews were initially selected based on title and abstract screening. After reading the full text, all systematic reviews were excluded (see the table with reasons for exclusion under the tab Methods).

Results

No systematic reviews or studies were included in the analysis of the literature that matched the predefined PICRO.

Summary of literature

Description of studies

No systematic reviews or studies were included in the analysis of the literature that matched the predefined PICRO.

Results

No systematic reviews or studies were included in the analysis of the literature that matched the predefined PICRO.

Level of evidence of the literature

GRADE was not performed, since no systematic reviews or studies were included in the analysis of the literature that matched the predefined PICRO.

Conclusions

- GRADE	Conclusions could not be drawn and GRADE was not performed, since no systematic reviews or studies were included in the analysis of the literature that matched the predefined PICRO.

Overwegingen - van bewijs naar aanbeveling

Uit de 40 potentieel relevante artikelen, die met de zoekvraag werden geïdentificeerd, konden voor deze richtlijnmodule geen relevante systematische literatuuronderzoeken of studies worden geïncludeerd die voldeden aan de vooraf gedefinieerde zoekvraag en selectiecriteria. Eén van de geïdentificeerde en gepubliceerde systematisch literatuuronderzoeken (Roberts, 2018) bevatte een onderzoeksvraag over de inzet van biopsie (versus herhaaldelijke beeldvorming) bij een niet te classificeren nodus ‘indeterminate nodule’ op beeldvorming met CT, MRI of CEUS. De plaats van de inzet van biopsie in de work-up wijkt in de vraag van Roberts (2018) enigszins af van de zoekvraag in deze richtlijnmodule. In deze richtlijnmodule was de vraag of biopsie ingezet zou kunnen ten opzichte van beeldvorming met MRI of CT. Roberts (2018) zocht naar studies waar biopsie werd ingezet na een niet te classificeren nodus op CT, MRI, of CEUS beeld. De literatuur over de inzet van biopsie als index test ten opzichte van beeldvorming middels MRI of CT als vergelijkende testen bij patiënten verdacht van een hepatocellulair carcinoom lijkt daarmee zeer schaars tot non-existent, als het gaat om een vergelijking tussen biopt en imaging voor diagnostiek levertumoren met als referentie (’gouden standaard’) klinische follow-up en/of resectie.

Internationale richtlijnen van de American Association for the Study of Liver Disease (AASLD) (Marrero, 2018), de European Association for the Study of the Liver (EASL) (EASL, 2018), en de European Society for Medical Oncology (ESMO) (Vogel, 2018) beschrijven de rol van het biopt in de diagnosestelling bij patiënten verdacht van hepatocellulair carcinomen.

Met betrekking tot patiënten met cirrotische levers, geeft de richtlijn van de EASL (2018) aan dat in LI-RADS categorieën die een hepatocellulair carcinoom niet uitsluiten (dat wil zeggen LR-2, LR-3, en LR-4) een biopsie van (ten minste) de grootste, dominante nodus uitgevoerd zou moeten worden. De EASL beschrijft ook het risico op vals negatieve uitslagen ('sampling error') bij biopten van kleine laesies, met name bij nodi <2 cm. De genoemde risico's van een biopt van een levertumor zijn bloedingen en entmetastasen, maar deze zijn volgens de EASL behandelbaar en komen niet vaak voor; max 1,4 % voor majeure bloeding en 0-2% voor entmetastasen (Boyum, 2019; Szpakowski, 2017; Huang, 1996; Maturen, 2006). Deze risico's zouden over het algemeen geen reden zijn om niet te biopteren (EASL, 2018). De EASL-richtlijn stelt dat een biopsie geïndiceerd is wanneer beeldvorming onduidelijk blijft bij patiënten met cirrose en vooral bij laesies kleiner dan twee centimeter (<2 cm). Ook wordt genoemd dat een biopsie van de laesie overwogen kan worden wanneer een hogere mate van zekerheid noodzakelijk is, zelfs wanneer aan de klassieke diagnostische parameters bij beeldvorming zijn voldaan. Het gepresenteerde diagnostische algoritme voor patiënten met cirrose in de EASL (2018) richtlijn plaatst het gebruik van een biopsie bij een nodus groter dan één centimeter ná negatieve uitslagen voor een hepatocellulair carcinoom van twee beeldvormende modaliteiten (dat wil zeggen multifasische CT met contrastmiddel, multifasische MRI met contrastmiddel, en MRI met gadolinium contrast). Er wordt onderbouwd dat de meerderheid van de nodi die kleiner zijn dan één centimeter veelal niet maligne blijken te zijn, en daarbij het afnemen van een biopt bij dergelijke kleine nodi grote kans geeft op sampling error (EASL, 2018). Het diagnostisch rendement is afhankelijk van de locatie van de laesie, differentiatie en de grootte van de nodus. Ook zijn de expertise van de biopteur en de patholoog van belang (EASL, 2018). In een eerdere prospectieve studie werd een positief biopt beschreven in 60% van levertumoren kleiner dan 2 cm (Forner, 2008). Herhaalde biopsie wordt door de EASL ondanks de lage evidentie sterk aanbevolen wanneer er onduidelijke bevindingen zijn, er discordante bevindingen zijn, of in het geval van een groei of verandering in het contrast-patroon tijdens de follow-up en de beeldvorming nog niet positief is voor een hepatocellulair carcinoom (EASL, 2018).

Met betrekking tot patiënten met niet-cirrotische levers acht de EASL dat alléén beeldvorming onvoldoende is en wordt dus een biopt geadviseerd. Ook bij patiënten waarbij onduidelijkheid bestaat over de aanwezigheid van cirrose zou de diagnostiek uitgevoerd moeten worden alsof er geen cirrose aanwezig is (EASL, 2018).

De richtlijn van de AASDL (Marrero, 2018) geeft met een zeer lage zekerheid een zwakke aanbeveling dat follow-up beeldvorming, beeldvorming met een alternatieve modaliteit of contrastmiddel, of biopsie toegepast zou kunnen worden bij patiënten met cirrose én een niet te classificeren nodus op beeldvorming zonder één van deze opties boven de anderen te kunnen aanbevelen. Met een zwakke aanbeveling en een zeer lage zekerheid stelt de AASDL (Marrero, 2018) voor om het biopt niet routinematig in te zetten bij elke niet te classificeren nodus. In de AASDL (Marrero, 2018) richtlijn wordt geschreven dat biopsie nodig kan zijn en het potentieel heeft een vroege diagnose te kunnen stellen, maar dat er ook risico bestaat op bloedingen en uitzaaiing/entmetatase. Ook bestaat er het risico dat een negatief resultaat toegekend kan worden aan een niet-representatief weefselmonster van de nodus, i.e. sampling error (Marrero, 2018). Er kan volgens de AASLD (Marrero, 2018) overwogen worden om een leverbiopt uit te voeren bij patiënten met een atypisch beeld voor hepatocellulair carcinomen op beeldvorming met contrastmiddel (LI-RADS 4), of bij patiënten met LI-RADS M laesie (c.q. maligniteit) om de precieze diagnose te stellen. Er wordt ten slotte gesteld dat de diagnose van een hepatocellulair carcinoom bij patiënten zonder cirrose niet zonder biopt kan worden gesteld (Marrero, 2018).

De richtlijn van de ESMO (European Society for Medical Oncology; Vogel, 2018) geeft aan dat een tweede biopsie, een andere beeldvormende modaliteit met contrastmiddel of een resectie van de laesie overwogen kan worden indien de eerste tumor biopsie geen focale laesie lijkt aan te tonen. Een tweede biopsie of een resectie zou overwogen kunnen worden bij patiënten met die in aanmerking komen voor een resectie met een acceptabel risico op morbiditeit en mortaliteit (Vogel, 2018). De ESMO-richtlijn stelt dat het belangrijk is om een gecombineerd hepatocellulair carcinoom met cholangiocarcinoom te onderscheiden van hepatocellulair carcinoom vanwege de potentiële verschillen in therapeutische opties. De richtlijn geeft aan dat gemengde tumordifferentiatiekenmerken bij een biopt wellicht niet zichtbaar zouden kunnen zijn (Vogel, 2018). Daarnaast zijn in zeer gedifferentieerde hepatocellulair carcinomen tekenen van maligniteit, zoals interstitiële of vasculaire invasie, veelal niet te detecteren via een biopsie volgens de richtlijn (Vogel, 2018). Ook de ESMO-richtlijn stelt dat de risico's van een biopsie (dat wil zeggen bloedingen en uitzaaiingen) niet vaak vóórkomen, behandelbaar zijn en dat dit het ziekteverloop en de algehele overleving niet beïnvloedt. De risico's zouden daarom geen reden moeten zijn om een diagnostisch biopt te ontzeggen volgens de ESMO (Vogel, 2018).

Samenvattend is een directe vergelijking tussen de diagnostische waarde van een biopt ten opzichte van imaging dus niet mogelijk op basis van de literatuur met als referentietest ('gouden standaard') een klinische follow-up en/of resectie. De indicatie voor biopt en eventueel resectie zal per patiënt afhangen van de context bij patiënten met cirrose: ontbreken kenmerkende beeldvorming, mate van verdenking, onzekerheid diagnose, grootte en locatie van de laesie. Voor niet-cirrotische levers is alléén beeldvorming niet voldoende en wordt dus een biopt geadviseerd. Voornoemde overwegingen kunnen per patiënt in het MDO worden besproken en gewogen.

<u>Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)</u>
Het belangrijkste doel van het verrichten van een tumor biopsie is meer zekerheid te krijgen over de diagnose. De belangrijkste voordelen van een biopt voor de patiënt zijn 1) zekerheid over de diagnose; 2) meer duidelijkheid omtrent de prognose; 3) ten behoeve van de verdere behandeling, oa biopt wenselijk respectievelijk vereist bij systeemtherapie en transplantatie bij non-cirrose. De belangrijkste nadelen van een biopt voor de patiënt zijn 1) het betreft een belastende interventie (punctie met dagopname); 2) er is een risico op complicaties 3) er is een risico dat de biopsie geen diagnose oplevert of dat de punctie niet mogelijk blijkt.

Waarden en voorkeuren van de patiënt dienen te worden besproken. Het is een individuele afweging of de patiënt de nadelen van het biopt tegen de voordelen vindt opwegen. Indien een biopt geen verdere consequenties heeft voor de behandeling kan hiervan in overleg met de patiënt worden afgezien.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
De indicatie voor biopt en eventueel resectie zal per patiënt afhangen van de context bij patiënten met cirrose: ontbreken kenmerkende beeldvorming, mate van verdenking, onzekerheid diagnose, grootte en locatie van de laesie. Voor niet-cirrotische levers is alléén beeldvorming niet voldoende en wordt dus een biopt geadviseerd. Voornoemde overwegingen kunnen per patiënt in het multidisciplinair overleg (MDO) worden besproken en gewogen.

Er is aangetoond dat de diagnostiek, inclusief classificerende diagnose en subclassificatie van levertumoren erg lastig kan zijn en afhankelijk is van exposure en expertise. Torbenson

(2019) toonde aan dat van de leverconsulten met betrekking tot levertumoren in consultverslag in 43% van de gevallen een concordante uitslag werd gerapporteerd, dat in 37% van de gevallen een meer specifieke diagnose kon worden gegeven en dat 17% van de inzendingen discordant was met betrekking tot initiële uitslag (ten aanzien van digniteit, in casu mate van zekerheid van goed- of kwaadaardigheid) (Torbenson, 2019). Een deel van de verschillen en/of aanvullingen met betrekking tot subtypering, kunnen worden verklaard door meer aanvullend onderzoek, beschikbaar in gespecialiseerde centra (Paterson, 2016; Rosmalen, 2021).

De werkgroep is derhalve van mening dat overwogen dient te worden de diagnostiek in samenspraak met gespecialiseerde centra (zie SONCOS normeringsrapport) te verrichten. Dit is van belang gezien de relatief lage incidentie van levertumoren en de complexe diagnostiek, met name in de differentiaaldiagnose van goed gedifferentieerde levertumoren, en ook in het licht van mogelijk gespecialiseerd aanvullend moleculair onderzoek en immuunhistochemische kleuringen. Hierbij kan paneldiagnostiek worden overwogen.

Aanbevelingen

Aanbeveling-1

Rationale van de aanbeveling

Een directe vergelijking tussen de diagnostische waarde van een biopt ten opzichte van imaging is niet mogelijk op basis van de literatuur met als referentietest (’gouden standaard’) een klinische follow-up en/of resectie. De indicatie voor biopt en eventueel resectie zal per patiënt afhangen van de context bij patiënten met cirrose: ontbreken kenmerkende beeldvorming, mate van verdenking, onzekerheid diagnose, grootte en locatie van de laesie.

Verricht geen tumor biopt bij patiënten met een cirrotische lever verdacht op een hepatocellulair carcinoom wanneer de laesie op beeldvorming voldoet aan de diagnostische kenmerken voor een hepatocellulair carcinoom (zie ook module 2 – plus referentie module 2). NB. Overweeg nadere diagnostiek inclusief biopt bij patiënten met een lage a priori kans voor HCC ondanks karakteristieke imaging, zoals bijvoorbeeld bij vasculaire cirrose/congestie.

Overweeg wel een biopt nadat in een MDO van een expertisecentrum (referentie SONCOS) is vastgesteld dat daar aanleiding voor is wat betreft de imaging in combinatie met klinische variabelen inclusief biomarkers (onder andere AFP).

Bespreek individuele overwegingen en voorkeuren ten behoeve van het besluit om wel of niet te biopteren met de patiënt, afhankelijk van behandelwens en behandelopties.

Aanbeveling-2

Rationale van de aanbeveling

Een directe vergelijking tussen de diagnostische waarde van een biopt ten opzichte van imaging is niet mogelijk op basis van de literatuur met als referentietest (’gouden standaard’) een klinische follow-up en/of resectie. Voor niet-cirrotische levers is alléén beeldvorming niet voldoende en wordt dus een biopt geadviseerd. Voornoemde overwegingen kunnen per patiënt in het MDO worden besproken en gewogen.

Verricht een tumor biopsie ter bevestiging van de diagnose bij patiënten met een niet-cirrotische lever verdacht op een hepatocellulair carcinoom, indien dit behandelconsequenties heeft.

Bespreek de beeldvorming, samen met de histologie, in een multidisciplinair overleg in een gespecialiseerd centrum.

Bespreek individuele overwegingen en patiëntvoorkeuren ten behoeve van het besluit om wel of niet te biopteren met de patiënt, afhankelijk van behandelwens en behandelopties.

Aanbeveling-3

Rationale van de aanbeveling

Om adequaat een biopt of resectiepreparaat te kunnen beoordelen, en resectiepreparaat te oriënteren en uit te kunnen snijden is het van belang dat adequate klinische info wordt verstrekt en waar van toepassing markeringen worden geplaatst en toegelicht.

Vermeld als klinisch aanvrager bij levertumoren de volgende items op het pathologie-aanvraagformulier:

- Aard van de resectie/type operatie.
- Mee gereseceerde structuren/organen (eventueel met markering).
- Lokalisatie tumor.
- Eventuele voorbehandeling (RFA, SIRT, TACE, TARE, anders).

Relevante voorgeschiedenis (incl. onderliggend leverlijden)

Als wordt overgegaan tot biopt en/of resectie volgt hieronder een beschrijving van de bewerking van het weefsel voor optimaal diagnostisch, therapeutisch en prognostisch rendement.

Bewerking weefsel na afname biopt en/of resectie

Doel van het pathologieverslag

Het Pathologieverslag bevat essentiële items, die van belang zijn voor behandeling, stadiering en prognose, zoals de tumorkenmerken: grootte, differentiatiegraad, groeiwijze, angioinvasie, radicaliteit, subtype tumor et cetera. Ook de aanwezigheid van positieve lymfeklieren en de status/mate van fibrose (gecomplementeerd door histochemische kleuringen bijvoorbeeld Sirius Rood, trichroom Masson) en steatose van het omringende leverparenchym hebben prognostische waarde (Serenari, 2020; Wang 2022, Mauro, 2022).

Eventueel consult/second opinion van een expertise centrum of van het leverpanel (Dutch Liver Pathology Panel; dlpp.nl) kan worden overwogen, inclusief voor specialistische kleuringen en NGS, alwaar van toepassing.

Geprotocolleerde verslaglegging

Het is aangetoond voor verschillende tumortypes dat geprotocolleerde verslaglegging leidt tot completere verslagen (Sluijter, 2016). De inzet is om met de in gebruik name van deze richtlijn, in samenwerking met Stichting PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief), een protocol te ontwikkelen voor synoptische rapportage van het hepatocellulair carcinoom.

Te vermelden items

In het pathologieverslag moeten ten minste alle items worden genoemd die nodig zijn voor het bepalen van het TNM-stadium (TNM8). Voor de status van relevante resectievlak(ken)

worden de definities gevolgd van de ICCR (International Collaboration on Cancer Reporting, iccr-cancer.org): R0 = geen residuale tumor (marge ≥ 1 mm), R1 = microscopische residuale tumor (marge <1mm), R2 macroscopische residuale tumor.

Bewerken van het preparaat

Voor het uitsnijden van leverresectiepreparaten is het belangrijk om zowel de laesie als het omringende leverparenchym te onderzoeken. Voor de beoordeling van de niet-tumoreuze lever wordt geadviseerd om op zo groot mogelijke afstand van de tumor (liefst t.m. >2 cm afstand) een coupe uit te nemen (om 'druk-effecten' van de tumor op het omringende leverweefsel te vermijden bij de beoordeling van de ernst onderliggend leverlijden).

In een (pre-)cirrhotische lever is het van belang om uit alle haarden te sampelen, die zich onderscheiden in termen van grootte, kleur en aspect voor de diagnostiek van foci van dysplasie en (vroeg) HCC.

Als de tumor < 2 cm is, wordt deze geheel ingesloten, met voor grotere tumoren 1 extra coupe per centimeter, waarbij het van belang is uit de gebieden te sampelen met verschillend/onderscheidend aspect. Coupes van de overgang tumor-omringend leverweefsel zijn van belang voor detectie van eventuele (micro)angioinvasie. De aanwezigheid van satellitose is geassocieerd met een hoger risico op recurrence. De WHO (5th ed) definieert satellitose als lesie(s) < 2 cm, aanwezig binnen 2 cm van een grotere, dominante nodus. Het aantal tumoren en de grootte van tumoren zijn prognostisch van belang bij HCC. Hoe groter het HCC, hoe meer kans op vaso-invasie en dedifferentiatie (Burt, 2020; WHO, 2019; TNM 8/Mauro, 2022).

Microscopische verslaglegging

Verschillende subtypes HCC zijn beschreven met soms onderscheidende morfologische en/of immuunhistochemische en/of moleculaire karakteristieken: steatohepatitisch HCC, heldercellig HCC, macrotrabeculair groeiend HCC (*geassocieerd met slechtere prognose*), scirrhous HCC, chomophoob HCC, fibrolamellair HCC (*with DNAJB1-PRKACA fusion*), neutrophil-rich and lymphocyte-rich HCC, progenitor HCC en gecombineerd hepatocellulair carcinoom-cholangiocarcinoom. Op dit moment heeft het subtyperen van HCC, inclusief moleculaire subtypes, nog geen eenduidige impact op klinisch beleid, behalve voor FL-HCC, vaak uitgesloten bij klinische trials en mengtumoren HCC-CC, die volgens CCA, danwel HCC protocollen worden behandeld, afhankelijk van dominante component (EASL, 2018; WHO, 2019; Montiri, 2022; Ziol, 2018; Calderaro 2017/2019,; Nault, 2013; Villanueva, 2011; Miltiadous, 2015).

De histologische diagnose van levertumoren wordt primair op basis van morfologie gesteld , conform de WHO criteria (WHO, 2019). In de differentiaal diagnose tussen dysplasie en HCC kan het nodig zijn aanvullend immunohistochemisch onderzoek te doen met aanvullende kleuringen voor Glypican3 (GPC3), Heat Shock Protein 70 (HSP70) en glutamine synthetase (GS). Als twee van de drie markers positief zijn heeft dat 70% sensitiviteit en 100% specificiteit voor HCC (Sciara, 2016). Ook kan mutatie analyse voor 'human telomerase reverse transcription' (hTERT) helpen om maligne transformatie te detecteren of mutaties voor beta-catenin, met name exon 3, die geassocieerd zijn met hoge kans op maligne ontaarding (Calderaro, 2017/2019; Ziol, 2018; Bioulac-Sage, 2017; EASL, 2016).

Voor aanvullend immunohistochemisch onderzoek in de differentiaaldiagnose tussen HCC en metastasen van onbekende primaire tumoren, wordt verwezen naar de richtlijn 'Primaire tumor onbekend'.

Overwegingen

Er kan worden overwogen aanvullende kleuringen te doen voor de detectie van progenitorcel karakteristieken, zoals keratine 19. In diverse studies is keratine 19 positiviteit geassocieerd met een slechtere prognose (EASL, 2018).

In de differentiaal diagnose tussen dysplasie en HCC kan het nodig zijn aanvullend immunohistochemisch onderzoek te doen met aanvullende kleuringen voor Glypican3 (GPC3), Heat Shock Protein 70 (HSP70) en glutamine synthetase (GS), zie ook de aanbevelingen uit de AASLD-richtlijn 2019 (Marrero, 2018) en EASL-richtlijn 2018 (EASL, 2018).

Aanbeveling-4

Rationale van de aanbeveling

Het Pathologieverslag van resectiepreparaten van maligne levertumoren, in casu hepatocellulair carcinoom, bevat essentiële items, die van prognostische betekenis zijn voor de patiënt en bepalend kunnen zijn voor het postoperatieve beleid. Het is van belang alle relevante parameters te identificeren en te benoemen in het verslag.

In het verslag moeten ten minste alle items worden genoemd die nodig zijn voor het bepalen van het TNM stadium. Daarnaast zijn moeten ook altijd de relevante prognostische parameters worden genoemd als daar zijn: perineurale groei, vaso-invasie, differentiatiegraad tumor, groeiwijze tumor, necrose/therapie effect bij voorbehandelde laesies, precursorlesies, onderliggend leverlijden. De radicaliteit van de resectie/resectiemarge is ook een belangrijke prognostische parameter.

Algemeen Pathologie

Gebruik zoveel mogelijk een standaardverslag; als mogelijk en beschikbaar, met gebruik van de PALGA Protocolmodule (PPM).

Vermeld voor een oncologische resectie van een hepatocellulair carcinoom de volgende aanvullende items in het pathologie verslag, waar van toepassing:

- *tumorgrootte (de maximale diameter van de grootste nodus);*
- *aantal en afmetingen overige tumorhaarden en indien van toepassing aanwezigheid satelietnodi, bij voorbehandelde noduli ihkv LTx ook diameter van het vitale tumor component vermelden;*
- *differentiatiegraad (advies; volgens WHO 2019);*
- *status resectiemarge;*
- *aan- of afwezigheid van vaso-invasieve groei;*
- *indien aanwezig kapseldoorbraak;*
- *status lymfeklieren, indien aanwezig;*
- *subtype HCC, if unequivocal (WHO 5^{e} ed) in het bijzonder macrotrabeculaire groei, indien aanwezig (>50% van de tumor met > 6 cellagen trabekeldikte) of (immunohistochemisch geïdentificeerd) progenitor karakteristieken (geassocieerd met slechtere prognose).*

Vermeld bij biopt:

- *indien aanwezig vaso-invasieve groei vermelden;*
- *het vermelden van een differentiatiegraad op biopsiemateriaal wordt niet aanbevolen (sampling- en representativiteitsprobleem), tenzij een weinig gedifferentieerd component herkenbaar is;*

- *op biopten kan eveneens het omringend leverweefsel worden beoordeeld indien dit aanwezig (cave representativiteit leverweefsel naast tumor) of separaat gebiopteerd is;*
- *subtype HCC, if unequivocal (WHO 5) in het bijzonder macrotrabeculaire groei, indien aanwezig (ten minste 1 focus > 6 cellagen trabekeldikte) of progenitor karakteristieken (geassocieerd met slechtere prognose).*

Overweeg, gezien de lage incidentie en de potentiele heterogeniteit in morfologie en subtypering van levertumoren, de diagnostiek in samenspraak met gespecialiseerde centra te verrichten. Hierbij kan paneldiagnostiek worden overwogen.

- NB 1. Radicaliteit, inclusief R-status (conform de definities ICCR): R0 = geen residuale tumor (marge ≥ 1 mm), R1 = microscopische residuale tumor (marge <1 mm), R2 macroscopische residuale tumor (R-2 is een klinische diagnose, gesteund door pathologisch onderzoek van de marge aan de patiënt zijde, met andere woorden dit kan alleen de chirurg interpreteren).
- NB 2. Er wordt geadviseerd in de conclusie van het pathologieverslag een beoordeling te vermelden van het omringende leverweefsel (op maximale afstand van de tumor, advies op t.m. afstand >2 cm indien mogelijk) in termen van gradering en stadiering (ontstekingsactiviteit, mate van steatose en mate van fibrose) in relatie tot het onderliggend lijden.

<u>Indien geen maligniteit kan worden aangetoond:</u>
Als er in resectiepreparaat of biopt geen (vitale) maligniteit kan worden aangetoond (na uitgebreid/volledig insluiten relevant gebied), dan moeten de overige gevonden afwijkingen in het verslag worden vermeld (inclusief beoordeling status leverparenchym, therapie-effecten, reactieve veranderingen en evt alternatieve verklaringen voor klinisch waargenomen haardvormige afwijzing).

T-stadium
T1a Solitaire tumor <= 2 cm met/zonder vaso-invasie
T1b Solitaire tumor > 2 cm zonder vaso-invasie
T2 Solitaire tumor > 2 cm of meerdere tumoren (waarbij geen van de separate laesies > 5 cm meet)
T3 Multipele tumoren met ten minste een laesie > 5 cm
T4 Tumor(en) met ingroei in vena porta/vena hepatica en/of directe ingroei in andere organen (inclusief diafragma). NB Ingroei galblaas en viscerale peritoneum zijn hierbij niet bedoeld.

N-stadium
Nx regionale lymfeklieren zijn niet beoordeelbaar
N0 Geen regionale lymfekliermetastasen
N1 Regionale lymfekliermetastasen aanwezig

M-stadium
M0 Geen metastasen op afstand
M1 Wel metastasen op afstand

Literatuur

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Bijlagen bij module 3

Kennislacunes

What is the diagnostic accuracy of a biopsy pro diagnosi compared to imaging (MRI or CT) to detect a hepatocellular carcinoma in patients with or without cirrhosis/liver disease, with pathology on resected material (for resectable patients) or a clinical follow-up (for unresectable patients) as a reference?

Interobserver variabiliteit, definitie van de diagnostische criteria en de klinische toepasbaarheid/relevantie (in de dagelijkse praktijk) van de verschillende HCC subtypes, inclusief moleculaire subtypes.

Predictieve en prognostische relevantie van de verschillende HCC subtypes, in het bijzonder bij patiënten met niet resectabele tumoren (wetenschappelijke literatuur heeft voornamelijk
patiënten met resectabele tumoren beschreven).

Evidence tables

No systematic reviews were included in the analysis of the literature that matched the predefined PICRO.

Table of excluded studies

Author and year	Reason for exclusion
Marquardt JU, Nguyen-Tat M, Galle PR, Wörns MA. Surveillance of Hepatocellular Carcinoma and Diagnostic Algorithms in Patients with Liver Cirrhosis. Visc Med. 2016 Apr;32(2):110-5. doi: 10.1159/000445407. Epub 2016 Apr 8. PMID: 27413728; PMCID: PMC4926879.	Narrative
Nadarevic T, Giljaca V, Colli A, Fraquelli M, Casazza G, Miletic D, Štimac D. Computed tomography for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease. Cochrane Database Syst Rev. 2021 Oct 6;10(10):CD013362. doi: 10.1002/14651858.CD013362.pub2. PMID: 34611889; PMCID: PMC8493329.	Biopsy as part of the reference test instead of being the index test
Nadarevic T, Colli A, Giljaca V, Fraquelli M, Casazza G, Manzotti C, Štimac D, Miletic D. Magnetic resonance imaging for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease. Cochrane Database Syst Rev. 2022 May 6;5(5):CD014798. doi: 10.1002/14651858.CD014798.pub2. PMID: 35521901; PMCID: PMC9074390.	Biopsy as part of the reference test instead of being the index test
Niu Y, Huang T, Lian F, Li F. Contrast-enhanced ultrasonography for the diagnosis of small hepatocellular carcinoma: a meta-analysis and meta-regression analysis. Tumour Biol. 2013 Dec;34(6):3667-74. doi: 10.1007/s13277-013-0948-z. Epub 2013 Jun 27. PMID: 23807679.	Biopsy as part of the reference test instead of being the index test
Roberts LR, Sirlin CB, Zaiem F, Almasri J, Prokop LJ, Heimbach JK, Murad MH, Mohammed K. Imaging for the diagnosis of hepatocellular carcinoma: A systematic review and meta-analysis. Hepatology. 2018 Jan;67(1):401-421. doi: 10.1002/hep.29487. Epub 2017 Nov 29. PMID: 28859233.	Different outcomes, patients seem tob e selected based on finding on CECT/MRI/CEUS instead of being suspected.
Sbeit W, Kadah A, Mari A, Mahamid M, Khoury T. A Comprehensive Narrative Review on the Evolving Role of Endoscopic Ultrasound in Focal Solid Liver Lesions Diagnosis and Management. Diagnostics (Basel). 2020 Sep 11;10(9):688. doi: 10.3390/diagnostics10090688. PMID: 32932960; PMCID: PMC7554970.	Narrative
Sbeit W, Kadah A, Mahamid M, Pellicano R, Mari A, Khoury T. A State-of-the-Art Review on the Evolving Utility of Endoscopic Ultrasound in Liver Diseases Diagnosis. Diagnostics (Basel). 2020 Jul 23;10(8):512. doi: 10.3390/diagnostics10080512. PMID: 32717886; PMCID: PMC7459648.	Narrative
Bruix J, Boix L, Sala M, Llovet JM. Focus on hepatocellular carcinoma. Cancer Cell. 2004 Mar;5(3):215-9. doi: 10.1016/s1535-6108(04)00058-3. PMID: 15050913.	Narrative

Chen X, Li M, Guo R, Liu W, Li J, Zong X, Chen Q, Wang J. The diagnostic performance of contrast-enhanced CT versus extracellular contrast agent-enhanced MRI in detecting hepatocellular carcinoma: direct comparison and a meta-analysis. Abdom Radiol (NY). 2022 Jun;47(6):2057-2070. doi: 10.1007/s00261-022-03484-7. Epub 2022 Mar 21. PMID: 35312822.	Biopsy as part of the reference test instead of being the index test
Colli A, Fraquelli M, Casazza G, Massironi S, Colucci A, Conte D, Duca P. Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. Am J Gastroenterol. 2006 Mar;101(3):513-23. doi: 10.1111/j.1572-0241.2006.00467.x. PMID: 16542288.	Biopsy as part of the reference test instead of being the index test
Colli A, Nadarevic T, Miletic D, Giljaca V, Fraquelli M, Štimac D, Casazza G. Abdominal ultrasound and alpha-foetoprotein for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease. Cochrane Database Syst Rev. 2021 Apr 15;4(4):CD013346. doi: 10.1002/14651858.CD013346.pub2. PMID: 33855699; PMCID: PMC8078581.	Biopsy as part of the reference test instead of being the index test
Cresswell AB, Welsh FK, Rees M. A diagnostic paradigm for resectable liver lesions: to biopsy or not to biopsy? HPB (Oxford). 2009 Nov;11(7):533-40. doi: 10.1111/j.1477-2574.2009.00081.x. PMID: 20495704; PMCID: PMC2785947.	Narrative
Durot I, Wilson SR, Willmann JK. Contrast-enhanced ultrasound of malignant liver lesions. Abdom Radiol (NY). 2018 Apr;43(4):819-847. doi: 10.1007/s00261-017-1360-8. PMID: 29094174.	Narrative
Filippi L, Braat AJ. Theragnostics in primary and secondary liver tumors: the need for a personalized approach. Q J Nucl Med Mol Imaging. 2021 Dec;65(4):353-370. doi: 10.23736/S1824-4785.21.03407-5. Epub 2021 Dec 9. PMID: 34881847.	Narrative
Fitzmorris P, Singal AK. Surveillance and Diagnosis of Hepatocellular Carcinoma. Gastroenterol Hepatol (N Y). 2015 Jan;11(1):38-46. PMID: 27099571; PMCID: PMC4836577.	Narrative
Forner A, Bruix J. The size of the problem: clinical algorithms. Dig Dis. 2013;31(1):95-103. doi: 10.1159/000347201. Epub 2013 Jun 17. PMID: 23797130.	Narrative
Fung KT, Li FT, Raimondo ML, Maudgil D, Mancuso A, Tibballs JM, Watkinson AA, Patch D, Burroughs AK. Systematic review of radiological imaging for hepatocellular carcinoma in cirrhotic patients. Br J Radiol. 2004 Aug;77(920):633-40. doi: 10.1259/bjr/31556748. PMID: 15326039.	Biopsy as part of the reference test instead of being the index test
Haider I, Amin B, Badshah A, Raza A. HEPATOCELLULAR CARCINOMA: MANAGEMENT UPDATE. Journal of Medical Sciences. 2019 Mar 29;27(1):52-60.	Narrative
Ichim VA, Chira RI, Mircea PA. Diagnostic yield of endoscopic ultrasound-guided biopsy of focal liver lesions. Med Pharm Rep. 2019 Jan;92(1):15-20. doi: 10.15386/cjmed-1066. Epub 2019 Jan 15. PMID: 30957081; PMCID: PMC6448489.	No relevant comparison
Iavarone M, Colombo M. HBV-related HCC, clinical issues and therapy. Dig Liver Dis. 2011 Jan;43 Suppl 1:S32-9. doi: 10.1016/S1590-8658(10)60690-1. PMID: 21195370.	Narrative
Juratli MA, Struecker B, Katou S, Morguel MH, Pascher A. Einfluss der Molekularpathologie auf die onkologische Chirurgie von Leber- und Gallengangstumoren (Influence of molecular pathology on oncological surgery of liver and bile duct tumors). Chirurg. 2021 Nov;92(11):1003-1010. German. doi: 10.1007/s00104-021-01495-6. Epub 2021 Sep 14. PMID: 34519849.	Article in German
Kaçar Özkara S, Ozöver Tuneli I. Fine needle aspiration cytopathology of liver masses: 101 cases with cyto-/histopathological analysis. Acta Cytol. 2013;57(4):332-6. doi: 10.1159/000351169. Epub 2013 Jul 12. PMID: 23860474.	Wrong comparison
Kim MJ. Current limitations and potential breakthroughs for the early diagnosis of hepatocellular carcinoma. Gut Liver. 2011 Mar;5(1):15-21. doi: 10.5009/gnl.2011.5.1.15. Epub 2011 Mar 16. PMID: 21461067; PMCID: PMC3065088.	Narrative
Lau WY, Lai EC. Hepatocellular carcinoma: current management and recent advances. Hepatobiliary Pancreat Dis Int. 2008 Jun;7(3):237-57. PMID: 18522878.	Wrong comparison
Li YW, Chen ZG, Wang JC, Zhang ZM. Superparamagnetic iron oxide-enhanced magnetic resonance imaging for focal hepatic lesions: systematic review and	Biopsy as part of the reference test instead of being the index test

meta-analysis. World J Gastroenterol. 2015 Apr 14;21(14):4334-44. doi: 10.3748/wjg.v21.i14.4334. PMID: 25892885; PMCID: PMC4394096.	
Lu L, Pan X. Accuracy of Non-Contrast MRI for the Detection of Hepatocellular Carcinoma: A systematic review and meta-analysis. Pak J Med Sci. 2022 Mar-Apr;38(3Part-I):743-750. doi: 10.12669/pjms.38.3.5142. PMID: 35480538; PMCID: PMC9002405.	Biopsy as part of the reference test instead of being the index test
Malek NP, Schmidt S, Huber P, Manns MP, Greten TF. The diagnosis and treatment of hepatocellular carcinoma. Dtsch Arztebl Int. 2014 Feb 14;111(7):101-6. doi: 10.3238/arztebl.2014.0101. PMID: 24622679; PMCID: PMC3957051.	Wrong comparison
Marrero JA. Multidisciplinary management of hepatocellular carcinoma: where are we today? Semin Liver Dis. 2013 Feb;33 Suppl 1:S3-10. doi: 10.1055/s-0033-1333631. Epub 2013 Mar 1. PMID: 23457037.	Narrative
Meijer K, Haagsma EB. HCV-related liver cancer in people with haemophilia. Haemophilia. 2012 Jan;18(1):17-24. doi: 10.1111/j.1365-2516.2011.02575.x. Epub 2011 Jun 9. PMID: 21651676.	Narrative
Mohanty S, Rajaram R, Bilimoria KY, Salem R, Pawlik TM, Bentrem DJ. Assessment of non-surgical versus surgical therapy for localized hepatocellular carcinoma. J Surg Oncol. 2016 Feb;113(2):175-80. doi: 10.1002/jso.24113. Epub 2015 Dec 10. PMID: 26662882.	Does not concern diagnosis
Korean Liver Cancer Study Group (KLCSG); National Cancer Center, Korea (NCC). 2014 Korean Liver Cancer Study Group-National Cancer Center Korea practice guideline for the management of hepatocellular carcinoma. Korean J Radiol. 2015 May-Jun;16(3):465-522. doi: 10.3348/kjr.2015.16.3.465. Epub 2015 May 13. PMID: 25995680; PMCID: PMC4435981.	Shows a diagnostic algorithm in a guidelines, does not concern a head-to-head comparison
Piñero F, Tanno M, Aballay Soteras G, Tisi Baña M, Dirchwolf M, Fassio E, Ruf A, Mengarelli S, Borzi S, Fernández N, Ridruejo E, Descalzi V, Anders M, Mazzolini G, Reggiardo V, Marciano S, Perazzo F, Spina JC, McCormack L, Maraschio M, Lagues C, Gadano A, Villamil F, Silva M, Cairo F, Ameigeiras B; Argentinean Association for the Study of Liver Diseases (A.A.E.E.H). Argentinian clinical practice guideline for surveillance, diagnosis, staging and treatment of hepatocellular carcinoma. Ann Hepatol. 2020 Sep-Oct;19(5):546-569. doi: 10.1016/j.aohep.2020.06.003. Epub 2020 Jun 25. PMID: 32593747.	Shows a diagnostic algorithm in a guidelines, does not concern a head-to-head comparison
Rodríguez-Perálvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. Ann Surg Oncol. 2013 Jan;20(1):325-39. doi: 10.1245/s10434-012-2513-1. Epub 2012 Nov 13. PMID: 23149850.	Wrong comparison
Suo L, Chang R, Padmanabhan V, Jain S. For diagnosis of liver masses, fine-needle aspiration versus needle core biopsy: which is better? J Am Soc Cytopathol. 2018 Jan-Feb;7(1):46-49. doi: 10.1016/j.jasc.2017.09.004. Epub 2017 Sep 21. PMID: 31043250.	Wrong comparison
Ma X, Zhan W, Zhang B, Wei B, Wu X, Zhou M, Liu L, Li P. Elastography for the differentiation of benign and malignant liver lesions: a meta-analysis. Tumour Biol. 2014 May;35(5):4489-97. doi: 10.1007/s13277-013-1591-4. Epub 2014 Jan 5. PMID: 24390668.	Biopsy as part of the reference test instead of being the index test
Yang D, She H, Wang X, Yang Z, Wang Z. Diagnostic accuracy of quantitative diffusion parameters in the pathological grading of hepatocellular carcinoma: A meta-analysis. J Magn Reson Imaging. 2020 May;51(5):1581-1593. doi: 10.1002/jmri.26963. Epub 2019 Oct 26. PMID: 31654537.	Biopsy as part of the reference test instead of being the index test
Ye F, Liu J, Ouyang H. Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid (Gd-EOB-DTPA)-Enhanced Magnetic Resonance Imaging and Multidetector-Row Computed Tomography for the Diagnosis of Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. Medicine (Baltimore). 2015 Aug;94(32):e1157. doi: 10.1097/MD.0000000000001157. PMID: 26266348; PMCID: PMC4616701.	Biopsy as part of the reference test instead of being the index test
Zeng K, Jiang Z, Yang J, Chen K, Lu Q. Role of endoscopic ultrasound-guided liver biopsy: a meta-analysis. Scand J Gastroenterol. 2022 May;57(5):545-557. doi: 10.1080/00365521.2021.2025420. Epub 2022 Jan 20. PMID: 35049405.	Wrong comparison

Literature search strategy

Algemene informatie

Richtlijn: NVMDL Hepatucellulair carcinoom	
Uitgangsvraag: Heeft diagnosticeren van een HCC met histologisch biopt pro diagnosi een betere accuratesse/toegevoegde waarde (voor- en nadelen) dan diagnosticeren met imaging in patiënten met levercirrose?	
Database(s): Ovid/Medline, Embase	Datum: 27-6-2022
Periode: nvt	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: HCC EN biopsy, pathology EN sensitivity, specificity Vanwege de hoge aantallen wordt gestart met de SRs. De twee sleutelartikelen worden gevonden.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 27-6-2022 met relevante zoektermen gezocht naar systematische reviews over het diagnosticeren van een HCC met histologisch biopt. De literatuurzoekactie leverde 199 unieke treffers op.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	192	47	199
RCTs			
Observationele studies			
Overig			
Totaal			

5

Zoekstrategie

Embase

No.	Query	Results
#13	#7 AND #12	2
#12	#10 OR #11	2
#11	28673446	1
#10	28859233	1
#9	pmid AND 28859233	0
#8	#6 AND #7	192
#7	#5 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)	4013
#6	'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	834494

	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	
#5	#3 AND #4	5016
#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	9238196
#3	#1 AND #2	5818
#2	'biopsy'/exp OR 'histopathology'/exp/mj OR biop*:ti,kw OR patholog*:ti,kw OR histopatholog*:ti,kw OR (((liver OR hepatic) NEAR/3 (puncture* OR biop*)):ti,ab,kw)	1206523
#1	'liver cell carcinoma'/exp OR ('liver cancer'/de AND 'primary tumor'/de) OR (((hepat* OR liver) NEAR/3 carcinom*):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw OR ((primary NEAR/3 liver):ti,ab,kw)	249725

Ovid/Medline

#	Searches	Results
8	6 and 7	47
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/))	573240
6	5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	2661
5	3 and 4	2766

4	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/	7424627
3	1 and 2	6755
2	exp Biopsy/ or exp Pathology/ or ((liver or hepatic) adj3 (puncture* or biop*)).ti,ab,kf. or patholog*.ti,kf. or histopatholog*.ti,kf.	575737
1	Carcinoma, Hepatocellular/ or (hepat* adj3 carcinom*).ti,ab,kf. or hepatocarcinom*.ti,ab,kf. or hepatoma.ti,ab,kf. or (liver adj3 primary).ti,ab,kf.	164919

Module 4 Prognostische factoren

Uitgangsvraag

Welke factoren zijn van belang bij het kiezen van een behandelstrategie voor patiënten met een onderliggende leveraandoening (zoals levercirrose) en een hepatocellulair carcinoom binnen de transplantatiecriteria?

Inleiding

Er is veel diversiteit op het gebied van de behandelstrategieën voor hepatocellulair carcinoom (HCC). Er is vooral praktijkvariatie bij patiënten met een HCC binnen de transplantatiecriteria (gebaseerd op het aFP-model) zonder metastasen: één tumor kleiner dan 5 cm, of minder dan vier haarden waarbij de tumors niet groter zijn dan 3 cm. In veel gevallen is transplantatie de beste optie wanneer de leverfunctie gecompromitteerd is. Echter is er een tekort aan donors. In deze module wordt uitgewerkt welke patiënten het meeste baat hebben bij een curatieve resectie en op basis van welke factoren deze patiënten gekozen kunnen worden.

Search and select

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

Which combination of patient characteristics predicts overall survival, disease-free survival, or overtreatment in patients with a hepatocellular carcinoma (HCC) meeting the Milan criteria undergoing hepatectomy?

P: patients with a diagnosed HCC meeting the criteria based on the aFP model (no metastases, one tumor smaller than 5 cm, or less than four lesions, each smaller than 3 cm);
I: prediction model with outcome overall survival, disease-free survival, or overtreatment;
C: other prediction model or no comparison;
O: model performance (discrimination parameters like concordance index (C-index), area under the curve, sensitivity, specificity, predictive value);
T: After diagnosis;
S: Secondary care and tertiary care.

<u>Relevant outcome measures</u>

The guideline development group considered C-index as a critical 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 performance of the included models as follows:

- 0.7≤ C-index <0.8: acceptable;
- 0.8≤ C-index <0.9: excellent;
- C-index ≥ 0.9: outstanding.

<u>Prognostic research: Study design and hierarchy</u>

When reviewing literature, there is a hierarchy in quality of individual studies. Preferably, the effectiveness of a clinical decision model is evaluated in a randomized clinical trial. Unfortunately, these studies are very rare. If not available, studies in which prediction models are developed and validated in other samples of the target population (external

validation) are preferred as there is more confidence in the results of these studies compared to studies that are not externally validated. Most samples do not completely reflect the characteristics of the total population, resulting in deviated associations, possibly having consequences for conclusions. Studies validating prediction models internally (e.g., bootstrapping or cross validation) can be used to answer the research question as well, but downgrading the level of evidence is obvious due to risk of bias and/or indirectness as it is not clear whether models perform sufficiently in target populations. The confidence in the results of unvalidated prediction models is very low. Therefore, such models will not be graded. This is also applicable for association models.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2010 until 11 May 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 145 hits. Studies were selected based on the following criteria:

- Being a systematic review.
- Reporting multivariable longitudinal association model or prediction model with outcome (overall survival, disease-free survival, or overtreatment) as dependent variable and independent variables (patient characteristics) determined before the start of the procedure.
- Models do not take independent variables into account that were determined after the start of the procedure.

Out of the initial 145 studies, 3 were selected based on title and abstract screening. After reading the full text, 2 studies were excluded (see the table with reasons for exclusion under the tab Methods), and one SR was included. In this SR, one described prognostic study (Yang, 2016) was relevant for the specific population defined in this clinical question, since this was the only validated model making predictions preoperatively.

Results

One prognostic 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

Yang (2016) developed two nomograms for pre- and postoperative prediction of long-term survival for patients who underwent hepatectomy for multiple hepatocellular carcinomas. The nomograms were built based on the results of multivariate analyses of OS on the pre- and postoperative data of 540 patients (median age 50 years, range 23 to 82; male 90%) extracted from a prospectively filled database from two institutions in China. A backward step-down selection process was used for the final model selection for the nomograms. Results were validated with an internal validation cohort (n=180) from the same database and an external validation cohort (n=180). Note that the nomograms were mainly based on the data of patients with HCC with HBV infection, which is the most common cause of HCC in China.

Only the preoperative nomogram was included in this literature analysis, as this nomogram could be used as a reference for patient selection for hepatectomy.

Results

Overall survival

Yang (2016) presented a preoperative nomogram including six relevant factors to predict overall survival:

- AFP, µg/L;
  - ≤20 (HR 1, reference);
  - 20-400 (HR 1.83 (95%CI 1.25 to 2.69));
  - >400 (HR 2.16 (95%CI 1.68 to 2.78)).
- HBV-DNA load, IU/mL;
  - ≤10^4 (HR 1, reference);
  - 10^4-10^6 (HR 1.55 (95%CI 1.13 to 2.13));
  - >10^6 (HR 1.86 (95%CI 1.41 to 2.45)).
- MELD score;
  - ≤8 (HR 1, reference);
  - 8-10 (HR 1.64 (95%CI 1.23 to 2.20));
  - >10 (HR 1.85 (95%CI 1.36 to 2.50)).
- Tumor number (HR 1.41 (95%CI 1.24 to 1.62)).
- Largest/smallest diameter (HR 1.05 (95%CI 1.00 to 1.11)).
- Total tumor diameter, cm (HR 1.07 (95%CI 1.03 to 1.11)).

The performance of the underlying model was reported by a C-index of 0.75 (95%CI 0.72 to 0.78). Calibration curves for the probability of 3- or 5-year survival showed an optimal agreement between prediction by the nomogram and the actual observation for the primary cohort, the internal validation cohort and the external validation cohort.

Disease-free survival

No studies reporting preoperative models predicting disease-free survival in patients undergoing hepatectomy for hepatocellular carcinoma were included in this literature analysis.

Overtreatment

No studies reporting preoperative models predicting overtreatment in patients undergoing hepatectomy for hepatocellular carcinoma were included in this literature analysis.

Level of evidence of the literature

Overall survival

The level of evidence regarding the outcome measure overall survival started at high and was downgraded by two levels because of study limitations (-1, risk of bias) and applicability (-1, bias due to indirectness).

Disease-free survival

No level of evidence could be determined as no studies reporting models predicting disease-free survival in HCC patients undergoing hepatectomy were included in this literature analysis.

Overtreatment

No level of evidence could be determined as no studies reporting models predicting overtreatment in HCC patients undergoing hepatectomy were included in this literature analysis.

Conclusions

Overall survival

Low GRADE	The evidence is uncertain about the performance of the model proposed by Yang (2016) (including factors AFP, HBV-DNA load, MELD score, tumor number, largest/smallest diameter and total tumor diameter) predicting overall survival in HCC patients undergoing hepatectomy. *Sources: (Yang, 2016)*

Disease-free survival

- GRADE	No evidence was found regarding the effect of different predictive factors on disease-free survival in HCC patients undergoing hepatectomy. *Source: -*

Overtreatment

- GRADE	No evidence was found regarding the effect of different predictive factors on overtreatment in HCC patients undergoing hepatectomy. *Source: -*

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 prestatie van (multivariabele) preoperatieve modellen die totale overleving, ziektevrije overleving en overbehandeling van patiënten met hepatocellulair carcinoom die een hepatectomie ondergaan. Er werden geen preoperatieve modellen gevonden die ziektevrije overleving en overbehandeling bij hepatectomie voorspellen. Wel werden er één intern en extern gevalideerd preoperatief model gevonden dat de totale overleving bij hepatectomie voorspelt. Vanwege een lage bewijskracht kan er geen uitspraak worden gedaan over de prestatie van dit model dat op basis van de factoren AFP, HBV-DNA lading, MELD score, aantal tumoren, grootste/kleinste diameter en totale tumor diameter de kans op totale overleving bij patiënten die resectie ondergaan voor meerdere hepatocellulair carcinomen voorspelt. De lage bewijskracht wordt voornamelijk veroorzaakt door beperkingen in de studieopzet ten aanzien van mogelijke uitvalsbias en het ontbreken van het corrigeren voor confounders. Daarnaast is er sprake van indirectheid omdat het geïncludeerde model voornamelijk gebaseerd (en extern gevalideerd) is op data van patiënten met hepatocellulair carcinoom met HBV-infectie, wat de meest voorkomende oorzaak van hepatocellulair carcinoom in China is.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

Bij het beoordelen van de waarden en voorkeuren van patiënten, en eventueel hun verzorgers, spelen verschillende factoren een rol. Ten eerste is het belangrijk om de risico's van zowel resectie als transplantatie te bespreken met de patiënt. Hoewel ze beide in principe curatief van opzet zijn, is er altijd een percentage patiënten dat een recidief krijgt na de behandeling. In principe is de kans op een recidief na transplantatie kleiner dan na resectie.

Daarnaast is het essentieel om het verwachtingspatroon van de patiënt in acht te nemen. Het is belangrijk om de patiënt goed voor te lichten over de wachtperiode en de kans op uitbreiding van het carcinoom. Als er meerdere opties beschikbaar zijn, zoals resectie en transplantatie, kan het raadzaam zijn om de patiënt door te verwijzen naar een

gespecialiseerd transplantatiecentrum. Daar kunnen de verschillende opties en de bijbehorende voor- en nadelen uitvoerig worden besproken.

In sommige gevallen is theoretisch gezien een levertransplantatie mogelijk, maar vanwege onderlinge afspraken met transplantatiecentra, die te maken hebben met een tekort aan donoren, komt de patiënt mogelijk niet direct in aanmerking voor een transplantatie. Het beleid kan per land verschillen, waarbij in sommige landen de vrijheid bestaat om op basis van een gedegen onderbouwing te kiezen voor het meest geschikte behandelingsplan.

Kosten (middelenbeslag)
Het is moeilijk de verschillende opties te vergelijken. Over het algemeen is levertransplantatie een duurdere procedure dan leverresectie. Een levertransplantatie vereist een complexe chirurgische ingreep, gevolgd door een langdurige postoperatieve zorg en intensieve immunosuppressieve medicatie om afstoting van het getransplanteerde orgaan te voorkomen.

Aan de andere kant is leverresectie een minder complexe procedure. Leverresectie vereist over het algemeen minder intensieve zorg en heeft daardoor vaak lagere kosten in vergelijking met een levertransplantatie.

Aanvaardbaarheid, haalbaarheid en implementatie
Alle patiënten die in aanmerking komen voor een transplantatie worden voorgelegd tijdens een MDO in het transplantatiecentrum. Hierbij is een multidisciplinaire aanpak van belang (zie ook module over wie er in een MDO aanwezig moet zijn).

Het richtsnoer LOL is reeds geïmplementeerd in Nederland.

Aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Voor het in aanmerking komen van een levertransplantatie is het richtsnoer LOL met name leidend. Uit de literatuur komen geen duidelijk gevalideerde prognostische factoren, maar de factoren die worden genoemd kunnen wel in acht worden genomen. Daarom is de aanbeveling voorzichtig geformuleerd en wordt het richtsnoer LOL als belangrijkste bron voor verwijzing genoemd.

Raadpleeg het LOL richtsnoer voor patiënten die een verhoogd risico hebben bij resectie, die in bepaalde gevallen in aanmerking komen voor transplantatie.

Overweeg resectie bij patiënten met HCC en cirrose bij wie geen verhoogd risico bestaat op complicaties bij een chirurgische interventie (Child-Pugh A zonder portale hypertensie met voldoende restleverfunctie). Hierbij kunnen de volgende factoren worden meegenomen:

- Aantal en grootte tumoren.
- Localisatie.
- AFP.

Literatuur

Beumer BR, Buettner S, Galjart B, van Vugt JLA, de Man RA, IJzermans JNM, Koerkamp BG. Systematic review and meta-analysis of validated prognostic models for resected hepatocellular carcinoma patients. Eur J Surg Oncol. 2022 Mar;48(3):492-499. doi: 10.1016/j.ejso.2021.09.012. Epub 2021 Sep 21. PMID: 34602315.

Yang P, Qiu J, Li J, Wu D, Wan X, Lau WY, Yuan Y, Shen F. Nomograms for Pre- and Postoperative Prediction of Long-term Survival for Patients Who Underwent Hepatectomy for Multiple Hepatocellular Carcinomas. Ann Surg. 2016 Apr;263(4):778-86. doi: 10.1097/SLA.0000000000001339. PMID: 26135698.

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Bijlagen bij module 4

Evidence tables

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Estimates of prognostic effect	Comments
Yang, 2016	**Type of study:** Cohort study To develop prognostic nomograms for patients undergoing hepatectomy for multiple hepatocellular carcinomas (mHCCs). **Setting and country:** Eastern Hepatobiliary Surgery Hospital in Shanghai, China. **Funding and conflicts of interest:** None declared.	**Inclusion criteria:** (1) 0 to 1 score of performance status, (2) no evidence of extrahepatic metastasis and macroscopic tumor invasion into major portal/hepatic veins, (3) no history of other malignancies, (4) no history of preoperative anticancer therapy, and (5) complete resection of macroscopic tumor nodules. **Exclusion criteria:** Patients who received palliative tumor resection, died of severe surgical complications, had incomplete clinical data, and lost to follow-up within 60 days after discharge were excluded. **N=** **Primary cohort:** 540	**Describe prognostic factor(s) and method of measurement:** Increased serum AFP level (20–400 μg/L: hazard ratio = 1.83; >400 μg/L: 2.16), higher HBV-DNA load (10^4–10^6 IU/mL: 1.55; >10^6 IU/mL: 1.86), higher MELD score (8–10: 1.64; ≥10: 1.85), more tumor numbers (1.41), larger total tumor diameter (TTD, 1.07), and larger ratio of the largest to the smallest tumor diameter (RLSD, 1.05) on imaging were independent risk factors of OS.	**Duration or endpoint of follow-up:** Patients were followed up once every 2 months for the first 2 years after discharge from hospitals and every 3 months thereafter. **For how many participants were no complete outcome data available?** **Primary cohort:** 11 (2%) **Internal validation cohort:** 8 (4%) **External validation cohort:** 0 **Reasons for incomplete**	**(Adjusted) Factor-outcome associations (include SEs or 95%CI and p-value if available):** See table 2. **Incremental predictive value[1]:** **Pre-operative model:** The C-index for OS prediction was 0.75 (95% confidence interval, 0.72 to 0.78). **Post-operative model:** The C-index for OS prediction was 0.80 (95% CI, 0.77 to 0.82). The C-indexes of the nomogram for predicting OS of patients with BCLC A- or B-stage mHCCs were 0.74 and 0.79, respectively.	Internal and external validation has been performed, nomogram has been made for both pre- and post-operative data.

		Internal validation cohort: 180 **External validation cohort:** 180 **Mean age ± SD:** **Primary cohort:** 50 (23-82) **Internal validation cohort:** 52 (27-77) **External validation cohort:** 54 (20-78) **Sex: % M / % F** **Primary cohort:** 90.4% / 9.6% **Internal validation cohort:** 88.8% / 11.2% **External validation cohort:** 88.3% / 11.7% **Potential confounders or effect modifiers**: Not reported.		**outcome data described?** Not reported.		

Risk of Bias Table

Study reference (first author, year of publication)	**Study participation**[1] Study sample represents the population of interest on key characteristics? (high/moderate/low risk of selection bias)	**Study Attrition**[2] Loss to follow-up not associated with key characteristics (i.e., the study data adequately represent the sample)? (high/moderate/low risk of attrition bias)	**Prognostic factor measurement**[3] Was the PF of interest defined and adequately measured? (high/moderate/low risk of measurement bias related to PF)	**Outcome measurement**[3] Was the outcome of interest defined and adequately measured? (high/moderate/low risk of measurement bias related to outcome)	**Study confounding**[4] Important potential confounders are appropriately accounted for? (high/moderate/low risk of bias due to confounding)	**Statistical Analysis and Reporting**[5] Statistical analysis appropriate for the design of the study? (high/moderate/low risk of bias due to statistical analysis)
Yang, 2016	Low risk of selection bias	Unclear: high risk of bias	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias

Table of excluded studies

Reference	Reason for exclusion
Al-Ameri AAM, Wei X, Wen X, Wei Q, Guo H, Zheng S, Xu X. Systematic review: risk prediction models for recurrence of hepatocellular carcinoma after liver transplantation. Transpl Int. 2020 Jul;33(7):697-712. doi: 10.1111/tri.13585. Epub 2020 Feb 25. PMID: 31985857.	This SR focused on prediction models after liver transplant, where we were interested in finding prediction models before resection
Peng Y, Wei Q, He Y, Xie Q, Liang Y, Zhang L, Xia Y, Li Y, Chen W, Zhao J, Chai J. ALBI versus child-pugh in predicting outcome of patients with HCC: A systematic review. Expert Rev Gastroenterol Hepatol. 2020 May;14(5):383-400. doi: 10.1080/17474124.2020.1748010. Epub 2020 May 20. PMID: 32240595.	This SR did not specifically focus on prediction models for resection or transplantation

Literature search strategy

Richtlijn: NVMDL HCC	
Uitgangsvraag: welke patiënten komen in aanmerking voor transplantatie/operatie (resectie)/minimaal invasieve interventie (lokale ablatie - interventieradiologen) of minimaal invasieve chirurgie (laparoscopie evt met robot)? Welke prognostische factoren zijn bepalend voor het kiezen tussen de behandelstrategieën?	
Database(s): Ovid/Medline, Embase	Datum: 11-5-2022
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 in eerste instantie gezocht met hepatocellulair carcinoom en een prognostisch filter. Het aantal gevonden referenties was helaas te groot, ca. 34.000. Daarna is geprobeerd om met de Milan criteria de set verder te beperken. Omdat 2 van de 4 sleutelartikelen hierdoor werden gemist is uiteindelijk besloten om een combinatie te maken met chirurgie. Daarmee zijn de elementen als volgt gedefinieerd: Hepatocellulair carcinoom EN chirurgie EN prognostisch filter Ook nu worden veel referenties gevonden, vandaar dat wordt besloten om te starten met het screenen van de SRs. Als geen relevante studies worden gevonden zullen later ook de andere studiedesigns moeten worden bekeken. Alle sleutelartikelen worden gevonden.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 11-5-2022 met relevante zoektermen gezocht naar systematische reviews en RCTs over de vraag welke pognostische factoren bepalend zijn voor de verschillende behandelstrategieën. De literatuurzoekactie leverde 145 unieke treffers op.	

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Module 5 Stereotactische radiotherapie bij HCC-patiënten met onderliggende levercirrose

Uitgangsvraag

Hoe presteert stereotactische radiotherapie als behandeling voor patiënten met hepatocellulair carcinoom met onderliggende levercirrose, in vergelijking met andere niet-operatieve lokale behandelingen?

Inleiding

Voor hepatocellulair carcinoom (HCC) is een beperkt aantal behandelingen beschikbaar. Stereotactische radiotherapie kan worden ingezet als alternatief voor TACE of andere lokale behandelmodaliteiten bij een selectieve groep patiënten. Het is onduidelijk hoe deze interventie presteert ten opzichte van andere behandelmogelijkheden. Radiotherapie wordt niet overal gebruikt, omdat niet overal bekend is dat dit een relevante behandeloptie kan zijn. In de praktijk leidt dit tot grote praktijkvariatie binnen Nederland.

Search and select

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

P: hepatocellulair carcinoma patients with liver cirrhosis (Child-Pugh score max B7 for cirrhosis, BCLC-A/B/C classification);
I: stereotactic body radiation therapy (SBRT);
C: other non-surgical local treatment options;
O: local tumor control, relapse rate, overall survival, toxicity, liver function.

Relevant outcome measures

The guideline development group considered **local tumor control, relapse rate and overall survival** as a critical outcome measure for decision making; and **toxicity and liver function** 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.

For **overall survival**, the working group defined >5% or >3% and a HR <0.7 as a minimal clinically (patient) important difference with a median follow-up of at least 3 years.

Search and select (Methods)

The databases (Medline (via OVID) and Embase (via Embase.com)) were searched with relevant search terms from 2005 until June 5th, 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 440 hits. Studies were selected based on the following criteria: SRs or RCTs, SBRT as one of the treatment arms. Seven studies were initially selected based on title and abstract screening. After reading the full text, 4 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 3 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

Shi

In the single-centered unblinded randomized study by Shi (2022), that was conducted in Shanghai, China, in total 76 adult patients with HCC were enrolled and randomized to the postoperative adjuvant SBRT arm or the surgery alone arm. Disease free survival and overall survival were compared between the groups (at one year, three years, and five years), and adverse events were monitored. The median follow-up period was 55 months.

Méndez Romero

In the multicenter unblinded RCT by Méndez-Romero (2023), conducted between 2015 and 2020 and coordinated by the Erasmus MC, 30 patients were randomized either to the TACE-DEB arm (transarterial chemoembolization delivered with drug eluting beads) or the SBRT-arm. Endpoints evaluated in this trial were time to progression, local control, overall survival, response rate, toxicity and quality of life. The number of participants was calculated as 100, however, due to slow accrual the trial was stopped when 30 participants were included. The median follow-up period was 28.1 months.

Comito

In the single-center unblinded randomized study by Comito (2022), That was conducted in the Humanitas Research Hospital in Rozzano, Milan, Italy, 40 patients were randomized to either the TAE/TACE arm or the SBRT arm, following multiple TAE/TACE courses. Endpoints were 1-year local control, 1-year progression free survival, distant recurrence-free survival, overall survival and the incidence of acute and late complications. The trial was closed prematurely due to slow accrual. The median follow-up period was 20 months.

Results

Local tumor control

In Shi (2022) no significant difference between the SBRT group (local recurrence 4/16) and the SA group (local recurrence 12/28) (p = 0.236) was reported. In Méndez-Romero et al., the median time to local recurrence was reported as 12.0 months in the TACE-DEB arm (95% CI, 4.9-not reached). In the SBRT arm it had not been reached (>40 months) HR = 0.15, (95% CI 0.02 to 1.21 p=0.075). In Comito et al., 2022, the use of SBRT was significantly correlated with superior LC as compared to TAE/TACE (median not reached versus 8 months, p = 0.0002; HR: 0.15 (CI95% 0.04 to 0.4)), corresponding to a 1-year LC of 84% versus 23%.

Relapse rate

No results were reported considering overall relapse rate.

Overall survival

In Shi (2022) the one-, three-, and five-year OS rates were 100%, 89.5%, and 75.0% in the SBRT group versus 100.0%, 68.4%, and 53.7% in the SA group, respectively (p = 0.053).

In Méndez-Romero (2023) the median OS time was 36.8 months in the TACE-DEB arm (95% CI, 18.1-not reached) and 44.1 months (95% CI, 20.3-not reached) in the SBRT arm (HR = 0.58, 95% CI 0.18 to 1.85, p=0.36). In Comito et al., the median OS time was 31 months (95% CI 22 to 53) in the SBRT arm and 30 months (95% CI 17–35) in the TAE/TACE arm (p = 0.472). OS at 1 and 2 years was 75% and 64% in the SBRT arm and 95% and 57% in the TACE arm, respectively.

Toxicity

In Shi et al (2022) this outcome was only measured for the SBRT-group, and not compared in the two study arms. In the SBRT-group, one patient developed abdominal pain, 2 abdominal distention, 2 dyspepsia, 3 nausea, 9 fatigue, 2 liver injury (ALT peak value 91.1 and 104.5 U/ml, respectively), 2 decreased leucocyte count, 2 decreased platelet count, and 1 anorexia.

In Méndez Romero (2023) two of the 16 patients in the TACE-DEB arm had between them a total of three episodes (13%) of grade ≥3 toxicity. In the SBRT group there were no such episodes. In the TACE-DEB arm, one patient developed an infection with sepsis within one month after treatment. One patient who developed a hepatobiliary disorder grade 3 (hepatic encephalopathy) between 1 and 3 months after treatment In the same period, the same patient developed an increase in bilirubin.

In the study by Comito (2022) the occurrence of toxicity was reported as infrequent (n = 5, 13%) and mainly consisted of grade 1–2 nausea and abdominal pain in 4 out of 5 patients (3 in the SBRT arm occurred during radiation treatment and 1 in the TAE/TACE arm occurred within 24 h of the embolization session). Only one patient experienced acute grade 3 sepsis complicated by pleural effusion following TACE. Overall, no grade >3 toxicity was observed in any treatment arm.

Liver function

No results were reported considering liver function.

Level of evidence of the literature

The level of evidence regarding the outcome measure local tumor control was downgraded with 3 levels: 2 levels because of study limitations (risk of bias), due to the unblinded setup of all included studies and premature termination of the trial due to slow accrual, and 1 level because of indirectness.

The level of evidence regarding the outcome measure overall survival was downgraded with 3 levels: 2 levels because of study limitations (risk of bias), due to the unblinded setup of all included studies and premature termination of the trial due to slow accrual, and 1 level because of indirectness.

The level of evidence regarding the outcome measure toxicity was downgraded with 3 levels: 2 levels because of study limitations (risk of bias), due to the unblinded setup of all included studies and premature termination of the trial due to slow accrual, and 1 level because of indirectness.

Conclusions

Very low GRADE	The evidence is very uncertain about the effect of SBRT on **local tumor control** when compared with other non-surgical interventions for hepatocellulair carcinoma patients with liver cirrhosis. *Sources: (Shi, 2022; Méndez Romero, 2023; Comito, 2022)*

Very low GRADE	The evidence is very uncertain about the effect of SBRT on **overall survival** when compared with other non-surgical interventions for hepatocellulair carcinoma patients with liver cirrhosis.

	Sources: (Shi, 2022; Méndez Romero, 2023; Comito, 2022)

Very low GRADE	The evidence is very uncertain about the effect of SBRT on **toxicity** when compared with other non-surgical interventions for hepatocellulair carcinoma patients with liver cirrhosis. *Sources: (Shi, 2022; Méndez Romero, 2023; Comito, 2022)*

- GRADE	No evidence was found on the effect of SBRT on **relapse rate** when compared with other non-surgical interventions for hepatocellulair carcinoma patients with liver cirrhosis. *Sources: (Shi, 2022; Méndez Romero, 2023; Comito, 2022)*

- GRADE	No evidence was found on the effect of SBRT on **liver function** when compared with other non-surgical interventions for hepatocellulair carcinoma patients with liver cirrhosis. *Sources: (Shi, 2022; Méndez Romero, 2023; Comito, 2022)*

Overwegingen – van bewijs naar aanbeveling

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

Stereotactische radiotherapie (SBRT) is op dit moment in Nederland een last resort behandeling bij een selectieve groep patiënten. Het valt niet binnen de standard of care, maar wordt ingezet als alternatief bij een specifieke groep die niet goed reageert op interventies als TACE.

Uit de drie RCT's die zijn gevonden in de systematische search kan niet met zekerheid worden geconcludeerd wat de effecten zijn van SBRT versus andere interventies. Dit heeft te maken met de kleine aantallen die zijn geïncludeerd, de langzame inclusie van patiënten waardoor twee van de drie trials eerder zijn gestopt dan tevoren gepland, en het open-label karakter van de studies, waardoor de evidentie minder zeker is.

De cijfers laten (met een onzekerheidsmarge) zien dat SBRT niet slechter lijkt te presteren bij het bereiken van lokale controle ten opzichte van TACE. Bovendien lijkt er geen toegenomen toxiciteit te zijn en is er vergelijkbare kwaliteit van leven in beide armen zoals onderzocht in de studie van Méndez Romero (2023). Daarom zou in overleg met patiënt, SBRT als behandelingsmodaliteit kunnen worden overwogen als alternatief voor TACE wanneer patiënten niet voor RFA in aanmerking komen, of als alternatief voor re-TACE wanneer na eerdere TACE radiologisch residu bestaat. Op basis van de beschikbare data komen in aanmerking: patiënten met Child-Pugh A of B7 levercirrose zonder ascites of encefalopathie die 1 HCC hebben van maximaal 6cm of maximaal 3 laesies tot cumulatieve diameter van 6cm.

Ook uit studies met een observationele opzet komt SBRT als behandeling naar voren die voor BCLC0-A patiënten wordt gezien als een alternatieve behandelingsoptie in ontwikkeling, voor ablatie en als brug naar transplantatie (Kim, 2020).

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

SBRT kan als alternatieve behandelingsmodaliteit worden aangeboden aan patiënten wanneer eerdere behandelingen met chirurgie, TACE of RFA geen of weinig effect hebben laten zien; zeker gezien deze geen slechtere kwaliteit van leven lijkt te veroorzaken en ook geen hogere kans op bijwerkingen. Het is van belang met de patiënt te bespreken wat de verwachtingen zijn van dit type behandeling als aanvulling op de standaardbehandelingen.

Kosten (middelenbeslag)

De behandeling bestaat over het algemeen uit 1 radiologische interventie voor markerplaatsing. Vervolgens 6 poliklinische sessies om de dag voor fractionele SBRT; kosten voor SBRT zijn ongeveer €7000,- De prijzen kunnen per centrum variëren. Deze kosten zijn niet significant afwijkend van alternatieven als TACE of SIRT.

Aanvaardbaarheid, haalbaarheid en implementatie

Technisch gezien kan in ieder centrum in Nederland dat SBRT uitvoert voor secundaire levertumoren, ook SBRT voor HCC-patiënten worden uitgevoerd. Er dient een goed protocol te zijn. De complexiteit van de patiënt met levercirrose en HCC leidt ertoe dat deze categorie patiënten over het algemeen in de bekende academische expertisecentra belandt, waar de noodzakelijke apparatuur aanwezig is. In een lokaal MDO wordt op basis van beschikbare expertise en wetenschappelijke data de meest geschikte behandelmodaliteit gekozen.

We verwachten gelijke toegang tot deze behandeling op basis van distributie van de expertisecentra. SBRT voor HCC is verzekerde zorg.

Aanbeveling

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

De evidentie van SBRT is gezien de beperkingen in het opzetten van studies moeilijk hoger te maken. Toch is de aanbeveling op basis van de beschikbare prospectieve en retrospectieve data wat sterker geformuleerd, omdat de patiënt er ten opzichte van andere behandelmodaliteiten geen nadelen van lijkt te ondervinden.

Overweeg stereotactische radiotherapie bij hepatocellulaircarcinoompatiënten als alternatieve behandelmodaliteit voor TACE wanneer zij niet voor RFA in aanmerking komen, of als alternatief voor re-TACE wanneer na eerdere TACE radiologisch residu bestaat.

Literatuur

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Bijlagen bij module 5

Kennislacunes

Een non-inferiority trial van SBRT versus TACE zou een goede aanvulling kunnen zijn op de huidige literatuur.

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Evidence tables

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Shi, 2022	**Type of study**: RCT, single center **Setting and country:** Eastern Hepatobiliary Surgery Hospital. Shanghai, China **Funding and conflicts of interest:** The research has received funding from the "Clinical science and technology innovation project of Shenkang Hospital Development Center" (SHDC12020104), Shanghai Jiading District	Inclusion criteria: - Adults who were diagnosed with HCC in BCLC stage 0 or A, - and had pathologically proved MVI in the surgical specimen, - and received marginal resection Exclusion criteria: - previous anti-tumour treatment - spontaneous rupture of tumour - re-resection for recurrence - delayed recovery from surgery (over 30 days)	Describe intervention (treatment/procedure/test): Stereotactic body radiotherapy (SBRT). A total dose of 35 Gy was delivered in a week.	Describe control (treatment/procedure/test): Surgery alone (SA): Conventional open partial hepatectomy.	Length of follow-up: Follow-up was measured at 1, 3 and 5 years. The median follow-up period was 55 months. Loss-to-follow-up: None Incomplete outcome data: None	Outcome measures and effect size (include 95%CI and p-value if available): **Overall survival** The one-, three-, and five-year OS rates were 100%, 89.5%, and 75.0% in the SBRT group versus 100.0%, 68.4%, and 53.7% in the SA group, respectively (p = 0.053). **Disease free survival** The one-, three-, and five-year DFS rates were 92.1%, 65.8%, and 56.1%	

	Fund'(2016-QN-001), and "Shanghai Municipal Health Commission Program" (202140362). The funding contributed to the job in the collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the article for publication. The authors state no further conflicts of interest.	N total at baseline: 76 Intervention: 38 Control: 38 Important prognostic factors[2]: *age ± SD:* *I: 56.42 (+/- 10.44)* *C: 55.74 (+/- 10.19)* *Sex:* *I: 86.8 % M* *C: 84.2 % M* **Groups comparable at baseline?** Yes, no differences between the two groups in terms of baseline characteristics and potential confounders.				in the SBRT group versus 76.3%, 36.8%, and 26.3% in the SA group, respectively (p = 0.005). **Adverse events** The overall incidence of radiotherapy-related AE was 31.6% (12 participants). **Local Recurrence** There is no significant difference between the SBRT group (local recurrence 4/16) and the SA group (local recurrence 12/28) (p = 0.236). **Distal intra-hepatic recurrence** The recurrence rate in the SA group (3/28) was not	

						significantly higher than the rate in the SBRT group (0/16) (p = 0.274). One participant in the SBRT group and two in the SA group had extra-hepatic recurrence after intra-hepatic recurrence in the follow-up period. No singly extra-hepatic recurrence occurred prior to intra-hepatic recurrence. **Toxicity** Only measured for the SBRT-group: One patient developed abdominal pain, 2 abdominal distention, 2 dyspepsia, 3 nausea, 9 fatigue, 2 liver injury (ALT peak value 91.1 and 104.5 U/ml, respectively), 2 decreased	

						leucocyte count, 2 decreased platelet count, and 1 anorexia.	
Méndez Romero, 2023	**Type of study**: RCT, multi center **Setting and country:** Coördination by Erasmus MC Cancer Institute **Funding and conflicts of interest:** Funding by Dutch Cancer Society, no conflicts of interest	Inclusion criteria: - Diagnosis HCC - (EASL–EORTC Clinical Practice Guidelines 2012) - Age ≥18 years - ECOG performance status 0-1 - BCLC stage A, B - None or cirrhosis Child Pugh A - Albumin>28 g/l - Bilirubin <50 µmol/l - INR <2.3 - AST/ALT <5 times ULN - Leukocytes >1.5x109/l - Hb >6 mmol/l - Preferably platelets ≥50x109/l - One to three tumors - Diameter (cumulative) ≤6 cm - Exclusion criteria:	A risk-adapted dose prescription of SBRT was applied with a maximum dose of 6x9 Gy (Canadian protocol), while 6x8 Gy was acceptable as lowest total dose.	Chemoembolization was performed by delivering DEB, i.e., hydrogel-based microspheres (Biocompatibles UK, Ltd, HepaSphere Biosphere Medical) loaded with the chemotherapeutic agent doxorubicin. If 1-month, 3-month or 6-month follow-up CT or MRI scan showed residual enhancement of the treated lesion, a second, third or even fourth TACE-DEB procedure was allowed.	Length of follow-up: Median follow-up 28.1 months Loss-to-follow-up: None Incomplete outcome data: None	Outcome measures and effect size (include 95%CI and p-value if available): **Time to progression** Median TTP was 12.0 months in the TACE-DEB arm (95% CI, 4.9-15) and 18.8 months in the SBRT arm (95% CI, 7.6-not reached) (HR = 0.45, 95% CI: 0.16-1.32, p=0.15). **Local control** Median time to local recurrence was 12.0 months in the TACE-DEB arm (95% CI, 4.9-not reached). In the SBRT arm it has not been reached (>40	Power analysis for this study calculated a needed sample size of 100 patients, but due to slow recruitment the study was closed after 30 patients. Two of the 30 included patients were retrospectively considered to be ineligible. Both these patients were randomized in the SBRT arm.

		- Uncontrolled portal hypertension. - Untreated esophageal varices Paquet III or IV - Ascites - Encephalopathy - Acute viral or non-viral hepatitis - Vascular tumor invasion - Previous radiotherapy to the liver - Pregnancy; - Distance from tumor to luminal organs <0.5 cm <u>N total at baseline</u>: 28 Intervention: 12 Control: 16 <u>Important prognostic factors</u>[2]: *age ± median range* *I: 62 (50-85)* *C: 69 (55-78)* *Sex:* *I: 10 (83%) M* *C: 14 (88%) M* **Groups comparable at baseline?**				months) HR = 0.15, (95% CI 0.02-1.21 p=0.075). **Overall survival** Median OS time was 36.8 months in the TACE-DEB arm (95% CI, 18.1-not reached) and 44.1 months (95% CI, 20.3-not reached) in the SBRT arm (HR = 0.58, 95% CI 0.18-1.85, p=0.36). **Response rate** Response rates were 81% (56% CR+25% PR) in the TACE-DEB arm and 92% (67% CR+25% PR) in the SBRT arm. **Liver transplantation** Nine patients had been treated with TACE-DEB with the intention of liver transplantation at a later	

		Yes, no differences between the two groups in terms of baseline characteristics				stage. Ultimately, five of these patients underwent transplantation. Median time from randomization to liver transplant was 10.7 months (range 9.8-17.1 months). The other patients were not transplanted, either because they did not wish to undergo transplantation (two patients) or due to disease progression (two patients). Six patients in the SBRT group were considered for liver transplant, four of whom ultimately received a transplant. Median time from randomization to liver transplant was 10.3 months (range 5.2-14 months). Due to	

						disease progression, two patients did not undergo a transplant. **Toxicity** Only considering adverse events that may have been related to the treatment delivered, two of the 16 patients in the TACE-DEB arm had between them a total of three episodes (13%) of grade ≥3 toxicity. In the SBRT group there were no such episodes. In the TACE-DEB arm, one patient developed an infection with sepsis within one month after treatment. This was scored as grade 4 and as probably related to the procedure. One patient who developed a hepatobiliary	

						disorder grade 3 (hepatic encephalopathy) between 1 and 3 months after treatment was also scored as possibly related. In the same period, the same patient, developed an increase in bilirubin. This was possibly related and scored as grade 3 (grade 2 at base line).	
Comito, 2022	**Type of study**: RCT, single center **Setting and country:** Humanitas Research Hospital, Rozzano, Italy **Funding and conflicts of interest:** No external funding received, no conflicts of interest declared	Inclusion criteria: Patients diagnosed with unresectable HCC by histology or non-invasive European Association for the Study of the Liver criteria following prior TAE or TACE with radiologically defined residual disease. Patients also had to be appropriate candidates for locoregional treatment with stage BCLC A-B HCC (without evidence of active extrahepatic disease, including vascular thrombi) and Child–Pugh Class A or B liver disease without existing encephalopathy or ascites.	In patients randomized to SBRT, a blank and contrast-enhanced 4D-simulated CT was acquired, and, when available, image fusion with magnetic resonance imaging and/or choline positron emission tomography for better target definition was performed. The clinical target volume (CTV) corresponded to the gross tumor volume, as delineated on pretreatment imaging. The planning target volume (PTV) corresponded to the clinical target volume plus a 7–10 mm isotropic expansion. Tumor motion was managed through 4D CT and	Patients randomized in the TAE/TACE arm were treated with TAE or conventional TACE according to the first embolization treatment received before the randomization. For TAE, the superselective catheterization of feeding vessels with microcatheters (Renegade High Flow; Boston Scientific, Natick, MA, USA) was obtained to perform subsegmental embolizations. Embolization was performed using small, precise and tightly calibrated microparticles (40 +/- 10 and/or 100 +/- 25 µm in	Length of follow-up: Median of 20 (range 3 to 56) months Loss-to-follow-up: One patient was lost before randomization Incomplete outcome data: None	Outcome measures and effect size (include 95%CI and p-value if available): **Local control** The use of SBRT was significantly correlated with superior LC as compared to TAE/TACE (median not reached versus. 8 months, p = 0.0002; HR: 0.15 (CI95% 0.04–0.4)), corresponding to a	All included patients have received one or more TAE/TACE course, and were unresponsive.

		Exclusion criteria: Patients were excluded from the trial in the event of concurrent malignancy, uncontrolled infection, severe anomalies in blood tests, previous abdominal irradiation and Grade _3 hemorrhagic complications within 4 weeks of enrollment in the study. N total at baseline: 40 Intervention: 21 Control: 19 Important prognostic factors[2]: *Sex:* *I: 71 % M* *C: 79 % M* **Groups comparable at baseline?** Yes, no significant differences between the groups	abdominal compression. SBRT was delivered in 3 to 6 fractions: the dose schedule was adapted on an individual basis in terms of the number of fractions and total delivered dose in order to prioritize with respect to dose–volume constraints for normal tissues, particularly the dose to the residual healthy liver.	diameter) with a hydrogel core and a nanothin coating of Polyzene-F (Embozene Color-Advanced Microspheres; CeloNova BioSciences, Newnan, GA, USA). The injection of 40 µm microspheres was performed until blood flow interruption or the administration of 4 mL. In the case of the residual enhancement and/or patency of feeding arteries, 100 _m microparticles were administered. In patients treated with TACE, 5 mL of iodized oil (Lipiodol) and 50 mg of epirubicin dissolved in 5 mL of non-ionic contrast media were used, followed by particle administration. The procedure was considered completed only when vascular shutdown was confirmed and no feeding vessels to the target tumor were detected at final angiography.		1-year LC of 84% versus. 23% **Progression free survival** Patients treated with SBRT experienced significantly longer PFS in comparison with patients treated with TAE/TACE (median 9 versus 4 months, p = 0.016; HR: 0.43 (CI95% 0.21–0.87)). **Distant Recurrence-Free Survival** Median DRFS was 14 months (95% CI 5–21) in the TAE arm and 9 months (95% CI 7–16) in the SBRT arm (p = 0.494). **Overall survival** Median OS was 31 months (95% CI 22–53) in the SBRT arm and 30	

						months (95% CI 17–35) in the TAE/TACE arm (p = 0.472). OS at 1 and 2 years was 75% and 64% in the SBRT arm and 95% and 57% in the TACE arm, respectively. **Patterns of failure** At the time of our analysis, local progression occurred in 21 patients following TAE/TACE (n = 15) or SBRT (n = 6). **Toxicity** The occurrence of toxicity was infrequent (n = 5, 13%) and mainly consisted of grade 1–2 nausea and abdominal pain in 4 out of 5 patients (3 in the SBRT arm occurred during radiation treatment and 1 in the TAE/TACE arm occurred within 24	

						h of the embolization session). Only one patient experienced acute grade 3 sepsis complicated by pleural effusion following TACE. Overall, no grade >3 toxicity was observed in any treatment arm.	

Risk of bias table

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

	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**
Shi, 2022	Definitely yes Reason: Randomization was carried out using the random sequence method of Excel on the computer, keeping a 1:1 ratio.	Definitely no Reason: Participants and study staff were unmasked to treatment allocation. Blinding was not applied.	Definitely no Reason: Patients and healthcare providers were not blinded. It is not mentioned whether the data collectors, outcome assessors and data analysts were blinded.	Definitely yes Reason: There was no loss to follow-up.	Definitely yes Reason: All relevant outcomes were reported.	Definitely yes Reason: No other problems noted	HIGH Reason: Lack of blinding, and unclear whether data collectors, outcome assessors and data analysts were blinded
Méndez Romero, 2023	Probably yes Reason: In this open-label, prospective, multicenter, randomized, phase 2 trial, we randomized patients 1:1 between TACEDEB (standard arm) and SBRT (experimental arm).	Definitely no Reason: Unblinded study (open label)	Definitely no Reason: Patients and healthcare providers were not blinded. It is not mentioned whether the data collectors, outcome assessors and data analysts were blinded.	Definitely yes Reason: There was no loss to follow-up.	Definitely yes Reason: All relevant outcomes were reported.	Definitely no The study was powered for 100 participants, but after 30 participants was stopped due to slow inclusion.	HIGH Lack of blinding, and unclear whether data collectors, outcome assessors and data analysts were blinded, trial underpowered and stopped prematurely due to slow inclusion
Comito, 2022	Definitely yes A computer-generated minimization program that incorporates a random element was used to ensure that the treatment groups were balanced for gender and Child-Pugh class	Definitely no Reason: Unblinded study (open label)	Definitely no Reason: Patients and healthcare providers were not blinded. It is not mentioned whether the data collectors, outcome assessors and data analysts were blinded.	Definitely yes Reason: There was no loss to follow-up.	Definitely yes Reason: All relevant outcomes were reported.	Definitely no The study inclusion was stopped prematurely due to slow accrual/number of events was met earlier than expected	HIGH Reason: Lack of blinding, and unclear whether data collectors, outcome assessors and data analysts were blinded, trial was stopped prematurely

Table of excluded studies

Reference	Reason for exclusion
Chen et al. Comparing stereotactic ablative radiotherapy (SABR) versus re-trans-catheter arterial chemoembolization (re-TACE) for hepatocellular carcinoma patients who had incomplete response after initial TACE (TASABR): a randomized controlled trial. BMC Cancer (2019) 19:275	Research protocol, no results
Kang et al. Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis. MOLECULAR AND CLINICAL ONCOLOGY (20140 2: 43-50	The intervention does not follow the PICO
Abdel-Rahman, Elsayed. External beamradiotherapy for unresectable hepatocellular carcinoma (Review). Cochrane Database of Systematic Reviews (2017) Issue 3	The intervention does not follow the PICO
Hoegen, P., Zhang, K.S., Tonndorf-Martini, E. et al. MR-guided adaptive versus ITV-based stereotactic body radiotherapy for hepatic metastases (MAESTRO): a randomized controlled phase II trial. Radiat Oncol 17, 59 (2022). https://doi.org/10.1186/s13014-022-02033-2	Population does not follow the PICO

Literature search strategy

Zoekverantwoording

Algemene informatie

Richtlijn: NVMDL Hepatocellulair carcinoom	
Uitgangsvraag: Hoe presteert stereotactische radiotherapie als behandeling voor patienten met hepatocellulair carcinoma met onderliggende lever cirrose, in vergelijking met andere gebruikte behandelingen?	
Database(s): Ovid/Medline, Embase	Datum: 14-4-2022, 5-6-2023
Periode: 2005-	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: 5-6-2023 Update en ontdubbeld t.o.v. vorige zoekstrategie uit 2022 14-4-2022 Voor deze vraag is gezocht met de volgende elementen: Levertumor AND stereotactische radiotherapie Twee van de drie sleutelartikelen worden niet gevonden: - Durand-Labrunie J, Baumann AS, Ayav A, Laurent V, Boleslawski E, Cattan S, Bogart E, Le Deley MC, Steen V, Lacornerie T, Peiffert D, Mirabel X. Curative Irradiation Treatment of Hepatocellular Carcinoma: A Multicenter Phase 2 Trial. Int J Radiat Oncol Biol Phys. 2020 May 1;107(1):116-125. doi: 10.1016/j.ijrobp.2019.12.004. Epub 2020 Jan 28. PMID: 32001057. - Takeda A, Sanuki N, Tsurugai Y, Iwabuchi S, Matsunaga K, Ebinuma H, Imajo K, Aoki Y, Saito H, Kunieda E. Phase 2 study of stereotactic body radiotherapy and optional transarterial chemoembolization for solitary hepatocellular carcinoma not amenable to resection and radiofrequency ablation. Cancer. 2016 Jul 1;122(13):2041-9. doi: 10.1002/cncr.30008. Epub 2016 Apr 8. PMID: 27062278. In overleg met de adviseur en de werkgroep wordt afgesproken dat toch alleen naar SRs en RCTs wordt gezocht. Op een later moment kan altijd een breder filter worden toegepast, als blijkt dat de juiste evidence niet wordt gevonden.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 5-6-2023 met relevante zoektermen gezocht vanaf 2005 naar systematische reviews en RCTs over stereotactische radiotherapie als behandeling van patiënten met levertumoren. De literatuurzoekactie leverde 440 unieke treffers op.	

Zoekopbrengst

5-6-2023	EMBASE	OVID/MEDLINE	Ontdubbeld t.o.v. Rayyan 14-4-2022
SRs	157	51	85
RCTs	177	108	63
Observationele studies			
Overig			
Totaal			440
14-4-2022	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs	123	41	132
RCTs	145	88	160
Observationele studies			
Overig			
Totaal			292

Zoekstrategie

Embase

No.	Query	Results
#23	#4 AND #21	**330**
#22	#13 AND #21 met breder filter sleutelartikelen wel gevonden.	**3**
#21	'controlled clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	**2929621**
#20	#4 AND #18	**955**
#19	#13 AND #18	**3**
#18	'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)))	**13040472**
#17	#14 NOT #16 2 sleutelartikelen niet gevonden	**2**
#16	#14 AND #15	**1**
#15	#7 OR #8	**268**

#14	#4 AND #13	**3**
#13	#10 OR #11 OR #12	**3**
#12	takeda AND 2016 AND chemoembolization:ti AND phase:ti	**1**
#11	sequential AND phase AND i AND ii AND trials AND of AND stereotactic AND body AND radiotherapy AND for AND locally AND advanced AND hepatocellular AND carcinoma AND sykes	**1**
#10	curative AND irradiation AND treatment AND of AND hepatocellular AND carcinoma AND 2020 AND durand	**1**
#9	#8 NOT #7	**145**
#8	#4 AND #6	**170**
#7	#4 AND #5	**123**
#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	**1899047**
#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 (1-1-2005)/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)	**2068**
#3	#1 AND #2	**3561**
#2	'stereotactic body radiation therapy'/exp OR 'sabr':ti,ab,kw OR 'sabrt':ti,ab,kw OR 'sbrt':ti,ab,kw OR (((stereotactic OR stereotaxic) NEAR/3 (therap* OR radiotherap* OR radiat*)):ti,ab,kw) OR radiosurg*:ti,ab,kw	**47184**
#1	'liver cell carcinoma'/exp OR 'liver tumor'/exp OR (((hepat* OR liver) NEAR/3 (carcinom* OR cancer* OR neoplasm* OR malignan*)):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw OR (((primary OR second*) NEAR/2 liver):ti,ab,kw)	**393360**

Ovid/Medline

#	Searches	Results
10	9 not 8	88
9	5 and 7	98
8	5 and 6	41
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/)	1367010
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	558807

	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/))	
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1254
4	limit 3 to yr="2005 -Current"	1328
3	1 and 2	1364
2	Radiosurgery/ or sabr.ti,ab,kf. or sabrt.ti,ab,kf. or sbrt.ti,ab,kf. or ((stereotactic or stereotaxic) adj3 (therap* or radiotherap* or radiat*)).ti,ab,kf. or radiosurg*.ti,ab,kf.	28363
1	exp Liver Neoplasms/ or ((hepat* or liver) adj3 (carcinom* or cancer or malignan* or neoplasm*)).ti,ab,kf.	235574

Module 6 Welke palliatieve systeemtherapie wordt geadviseerd bij patiënten met een (niet lokaal behandelbaar)-HCC?

Uitgangsvraag
Welke palliatieve systeemtherapie wordt geadviseerd bij patiënten met een (niet lokaal behandelbaar)-HCC?

Inleiding
In de vorige richtlijnen was sorafenib de enig geregistreerde palliatieve behandeling voor het HCC. Nadien zijn er meerdere middelen in eerste en tweede lijn onderzocht en geregistreerd. Het doel van de module is de plaatsbepaling van deze middelen in de Nederlandse situatie te beschrijven.

Search and select
A systematic review of the literature was performed to answer the following question:
Which treatment is to be advised for patients with (unresectable) HCC?

PICO
P: non-locally-treatable *patients with a diagnosis of hepatocellular carcinoma;*
I: systemic therapy;
C: other systemic therapy or placebo;
O: overall survival, progression-free survival, response rate, adverse events, quality of life.

Relevant outcome measures
The guideline development group considered overall survival and progression-free survival as a crucial outcome measure for decision making; and response rate, complications/adverse events and quality of life as important outcome measures for decision making.

The guideline development group defined the outcome measures as follows:

Overall survival (OS)	Time from randomisation to death from any cause, with a minimum follow-up of 1 years
Progression-free survival (PFS)	Time from randomisation or initiation of treatment to the occurrence of disease progression or death, with a minimum follow-up of 1 year
Tumour response rate (TRR)	Tumour response rate, with a minimum follow-up of 1 year
Adverse events (AE)	Grade ≥ 3
Quality of life (QoL)	Overall QoL, measured with a validated and reliable instrument

Clinically relevant difference
The guideline development group defined a minimal clinically relevant difference at a minimum of weeks) *(in line with "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)")* of:
- Overall survival: >12 weeks or HR <0.7.
- Progression-free survival: >12 weeks or HR <0.7.

And, in case of absence of a clinically relevant difference in overall survival or progression-free survival:
- Response rate: >20% difference.
- Quality of life: A minimal clinically important difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Adverse events: <25% difference.

Data-synthesis
Results from RCTs studies were described and synthesized (preferably by meta-analysis) separately.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until April 15th, 2022. The detailed search strategy is depicted under the tab Methods.
The systematic literature search resulted in 1115 hits. Studies were selected based on the following criteria:

- included patients HCC, ineligible for surgical intervention;
- compared systemic therapy;
- reported at least one of the outcomes of interest;
- the study design is a systematic review (SR) (preferably of randomized controlled trials; RCTs), or RCT;
- written in English language.

Based on title and abstract screening, 14 studies were initially selected. After reading the full text and thorough assessment of the studies, 11 studies were excluded (see table with reasons for exclusion under the tab Methods), and 3 systematic reviews were included.

Results
A total of three studies were included in the analysis of the literature. The 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.

Not all systemic therapies are included in the literature summary. The Committee BOM (cieBOM) makes recommendations about the procedure on the basis of the evidence relating to its efficacy and safety. Therefore, we will answer the question which of the available therapies in the Netherlands is the most effective and safe in patients with (unresectable) HCC in the first-line, second-line and third-line. An overview of all the included RCTs in the systematic reviews and the selected RCTs can be found in table 6.1 and table 6. 2.

The first line available treatments in the Netherlands are:

- Sorafenib.
- Atezolizumab + Bevacizumab.
- Lenvatinib.

The second- and further line available treatments in the Netherlands are:

- Sorafenib (add-on).
- Regorafenib.

Currently, no drugs of proven efficacy in the third-line settings are available in the Netherlands.

Summary of literature
Park (2021) performed a systematic review and network meta-analyses (NMA) to evaluate the efficacy and safety of various systemic therapies in advanced hepatocellular carcinoma (HCC) in the first line and second line setting. Inclusion criteria were RCTs with head-to-head comparisons of at least two arms; systemic therapy in the first line or second line or later setting for advanced or metastatic HCC; and had at least one of the following clinical outcomes: objective response rate (ORR), progression-free survival (PSF) or time to progression if PFS was not reported. Three databases (PubMed, Embase, Cochrane) were searched up to April 2020. 13 first-line and 11 second-line trials were included in the final quantitative and qualitative synthesis.

Oranratnachai (2021) performed a systematic review and network meta-analyses (NMA) to evaluate the efficacy and safety of various systemic therapies in advanced hepatocellular carcinoma (HCC) in the first-line setting. Inclusion criteria were RCTs who included adults with advanced HCC who were treatment-naïve; comparing any pair of chemotherapy agents, MKIs, or placebo; and had at least one of the following clinical outcomes: OS, PFS, ORR and AE. Two databases (PubMed and SCOPUS) were searched up to November 30, 2019. 20 first-line studies were included in the final quantitative and qualitative synthesis.

Solimando (2022) performed a systematic review and network meta-analyses (NMA) to evaluate the efficacy and safety of various systemic therapies in advanced hepatocellular carcinoma (HCC) in the first-line setting. Inclusion criteria were RCTs who included adults with advanced HCC who were already treated with sorafenib; receiving a second-line systemic treatment in a phase II or phase III RCT; and had at least one of the following clinical outcomes: OS, PFS and drug withdrawal due to adverse events. Four (PubMed, SCOPUS, Web of Science, and ClincialTrials.gov) were searched up to December 31, 2020. 14 second- line studies were included in the final quantitative and qualitative synthesis.

Table 6.1 Overview and characteristics of the included studies evaluating the first-line treatments in the selected systematic reviews

RCT	Year	Trial/Phase	Intervention	Comparison	N	Park (2021)	Oranratnachai (2021)
Llovet	**2008**	**SHARP/III**	**Sorafenib**	**Placebo**	**602**	**X**	**X**
Cheng	**2009**	**NCT00492752/III**	**Sorafenib**	**Placebo**	**226**	**X**	**X**
Cheng	2013	SUN1170/III	Sunitinib	Sorafenib	1074	X	X
Johnson	2013	BRISK-FL/III	Brivanib	Sorafenib	1155	X	X
Zhu	2015	SEARCH/III	Erlotinib + Sorafenib	Sorafenib	720	X	X
Cainap	2015	NCT01009593/III	Linifanib	Sorafenib	1035	X	X
Cheng	2015	NCT01033240/II	Tigatuzumab + Sorafenib	Sorafenib	162	X	X
Kudo	2017	NCT02400788/II	Resminostat + Sorafenib	Sorafenib	-	X	
Kudo	**2018**	**REFLECT/III**	**Lenvatinib**	**Sorafenib**	**954**	**X**	**X**
Yau	2019	CheckMate 459/III	Nivolumab	Sorafenib	743	X	
Abou-Alfa	2019	CALGB80802/III	Sorafenib + Doxorubicin	Sorafenib	356	X	X
Finn	**2020**	**IMbrave150/III**	**Atezolizumab + Bevacizumab**	**Sorafenib**	**485**	**X**	
Bi and Qin	2020	NCT02645981/II-III	Donafenib	Sorafenib	659	X	
Lai	1988	-/III	Doxorubicin	No treatment	106		X
Mok	1999	-/II	Nolatrexed	Doxorubicin	54		X
Yeo	2005	-/III	PIAF	Doxorubicin	188		X
Gish	2007	-/III	Nolatrexed	Doxorubicin	445		X
Qin	2013	NCT00471965 /III	FOLFOX4	Doxorubicin	371		X
Ji*	2013	-/III	Sorafenib	No treatment	189		X
Palmer	2018	NCT01004003 /II	Nintedanib	Sorafenib	93		X
Thomas	2018	NCT00881751/II	Bevacizumab + Erlotinib	Sorafenib	90		X
Yen	2018	NCT00987935 /II	Nintedanib	Sorafenib	95		X
Assenat	2019	PRODIGE 10/II	Sorafenib + GEMOX	Sorafenib	95		X
Koeberle	2016	SAKK77/08 and SASL 29/II	Sorafenib + Everolimus	Sorafenib	105		X

In **bold** the selected RCTs which are based on available therapies in the Netherlands

*Child-Pugh Class B population

Table 6.2 Overview and characteristics of the included studies evaluating the second-line treatments in the selected systematic reviews

RCT	Year	Trial/Phase	Intervention	Comparison	N	Park (2021)	Solimando (2021)
Bruix	**2017**	**RESORCE/III**	**Regorafenib**	**Placebo**	**573**	**X**	**X**
Abou-Alfa	2018	CELESTIAL/III	Cabozantinib	Placebo	707	X	X
Zhu	2015	REACH/III	Ramucirumab	Placebo	644	X	X
Zhu	2019	REACH-2/III	Ramucirumab	Placebo	292	X	X
Li (Qin)	2020	NCT02329860/III	Apatinib	Placebo	393	X	
Finn	2019	KEYNOTE-240/III	Pembrolizumab	Placebo	413	X	X
Llovet	2013	BRISK-PS/III	Brivanib	Placebo	395	X	X
Santoro	2013	NCT00988741/II	Tivantinib	Placebo	107	X	X
Zhu	2014	EVOLVE-1/III	Everolimus	Placebo	546	X	X
Kang	2015	NCT01210495/II	Axitinib	Placebo	202	X	X
Rimassa	2018	RESORCE/III	Tivantinib	Placebo	340	x	
Abou-Aifa	2016	NCT01507168/III	Codrituzumab	Placebo	185		X
Kudo	2017	S/CUBE/III	S-1	Placebo	333		X
Abou-Aifa	2018	ADIPEG20/III	ADIPEG240	Placebo	635		X
Rimassa	2018	METIV-HCC/III	Tivantinib	Placebo	340		X
Kudo	2020	JET-HCC/III	Tivantinib	Placebo	195		X

In **bold** the selected RCT which is based on available therapies in the Netherlands

First-line treatment
Four RCTs were selected that assessed the systemic therapy in the first-line setting.

Sorafenib versus placebo was studied in two RCTS (Llovet, 2008; Cheng, 2009). Lenvatinib versus sorafenib was studied in one RCT (Kudo, 2018). Atezolizumab + bevacizumab versus sorafenib was studied in 1 RCT (Finn, 2020) (see table 6.1).

Second-line treatment
1 RCT was selected that assessed the systemic therapy within the second-line setting.

This study assessed the efficacy and safety of regorafenib in patients with HCC who have progressed during sorafenib treatment (Bruix, 2017) (see table 6.2).

Third-line treatment
No studies reporting efficacy and safety of third-line treatment in patients with (unresectable) HCC were included in this literature review.

Description of studies
Subquestion 1 – Which first line systemic therapy is the most effective and safe for use in patients with (unresectable) HCC?
Sorafenib versus placebo
Llovet (2008) - SHARP described a phase III, double-bind, placebo-controlled trial, which was conducted in 21 countries (121 sites) in Europe, North America, South America, and Australasia. They evaluated the efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma who had not received previous systemic therapy. A total of 602 patients were randomized to receive sorafenib (n=299) at a dose of 400 mg twice daily or placebo (n=303). The mean (SD) age was 64.9 (11.2) years in the intervention group, compared with 66.3 (10.2) years in the control group. In the intervention group 260/299 (87%) were males, compared with 264/303 (87%) in the control group. All patients had a Child-Pugh class A score. The following relevant outcome measures were included: overall survival, time to symptomatic progression, objective response (partial/complete), adverse events. This RCT was included in the systematic review by Park (2021) and Oranratnachai (2021).

Cheng (2009) - described a phase III, double-bind, placebo-controlled trial, which was conducted in 23 sites within the Asia-Pacific region, in China, Taiwan, and South-Korea. They evaluated the efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma who had not received previous systemic therapy. A total of 226 patients were randomized to receive sorafenib (n=150) at a dose of 400 mg twice daily or placebo (n=76). The median (range) age was 51 (23-86) years in the intervention group, compared with 52 (25-79) years in the control group. In the intervention group 127/150 (84.7%) were males, compared with 66/76 (86.8%) in the control group. All patients had a Child-Pugh class A score. The following relevant outcome measures were included: overall survival, time to progression, objective response (partial/complete), adverse events, quality of life. This RCT was included in the systematic review by Park (2021) and Oranratnachai (2021).

Atezolizumab + Bevacizumab versus Sorafenib
Finn (2020) – IMbrave150 described a phase III, global, open-label randomized controlled trial, which was conducted at 111 sites in 17 countries. They evaluated the efficacy and safety of atezolizumab plus bevacizumab compared to sorafenib in patients with advanced hepatocellular carcinoma who had not received previous systemic therapy. A total of 573 patients were randomized to receive atezolizumab (IV, 1200 mg on day 1 of each 21-day cycle) plus bevacizumab (IV, 15 mg/kg on day 1 of each 21 day cycle (n=336), compared with sorafenib (orally administered 400 mg twice per day on days 1-21 of each 21-day cycle) (n=165). In the intervention group 277/336 (82%) were males, compared with 137/165 (83%) in the control group. All patients had a Child-Pugh class A score. The

following relevant outcome measures were included: overall survival, progression-free survival, objective response (partial/complete), adverse events, quality of life. This RCT was included in the systematic review by Park (2021) and Oranratnachai (2021). After the search date, a recent update became available which present updated data after 12 months of additional follow-up **(Cheng, 2022)**. This study is added to the evidence table and data-synthesis.

Lenvatinib versus Sorafenib

Kudo (2018) – REFLECT described a phase III, open-label, randomized controlled non-inferiority trial which was conducted at 154 sites in 20 countries throughout the Asia-Pacific, European, and North American region. They compared the overall survival in patients treated with lenvatinib versus sorafenib in patients with advanced hepatocellular carcinoma who had not received previous systemic therapy. A total of 954 patients were randomized to receive lenvatinib (12 mg/day for bodyweight ≥60 kg or 8 mg/day for bodyweight) (n=478) or sorafenib 400 mg twice-daily in 28-day cycles (n-476). In the intervention group 405/478 (85%) were males, compared with 401/476 (84%) in the control group. All patients had a Child-Pugh Class A score. The following relevant outcome measures were included: overall survival, progression-free survival, objective response (partial/complete), adverse events, quality of life.

Subquestion 2 – Which second line systemic therapy is the most effective and safe for use in patients with (unresectable) HCC?

Regorafenib versus placebo

Bruix (2017) - RESORCE described a phase III, double-bind, placebo controlled trial, which was conducted in 21 countries (152 sites) in North America, South America, Europe, Asia, and Australia. They evaluated the efficacy and safety of regorafenib in patients with advanced hepatocellular carcinoma who tolerated sorafenib (≥400 mg/day for ≥20 of last 28 days of treatment) and progressed on sorafenib. A total of 573 patients were randomized to receive regorafenib at a dose of 160 mg every day for 3 weeks of every 4-week cycle plus best supportive care (n=379) or placebo + best supportive care (n=194). The median (range) age was 64 (54-71) years in the intervention group, compared with 62 (55-68) years in the control group. In the intervention group 333/379 (88%) were males, compared with 171/194 (88%) in the control group. All patients had a Child-Pugh class A score. The following relevant outcome measures were included: overall survival, progression-fee survival, objective response (partial/complete), adverse events. This RCT was included in the systematic review by Park (2021) and Solimando (2022).

Subquestion 3 – Which third line systemic therapy is the most effective and safe for use in patients with (unresectable) HCC?

No studies reporting efficacy and safety of third-line treatment in patients with (unresectable) HCC were included in this literature review.

The Celestial study was not included as patients with both second- and third-line treatment were permitted without preplanned subpopulations efficacies.

First-line treatment
Overall survival (OS) (crucial)
Sorafenib versus placebo
Two studies (Llovet, 2008; Cheng, 2009) reported the median overall survival.

Llovet (2008) reported OS, which was measured from the date of randomization until the date of death from any cause. The median OS was 10.7 months in the intervention group, compared with 7.9 in de control group. This resulted in a HR of 0.69 (95% CI 0.55 to 0.87). This difference is considered clinically relevant.

Cheng (2009) reported OS, which measured from the date of randomization until the date of death from any cause. The median OS was 6.5 in the intervention group, compared with 4.2 in the control group. This resulted in a HR of 0.65 (95% CI 0.53 to 0.81). This difference is considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the studies were RCTS. The level of evidence was downgraded by 2 levels, because of study limitations (risk of bias, -1 (see RoB assessment)) and because the optimal information was criteria is not met (imprecision, -1). Therefore, the level of evidence for the outcome 'overall survival' is considered *low.*

Atezolizumab + Bevacizumab versus Sorafenib
Cheng (2022) reported OS, which measured from the date of randomization until the date of death from any cause. The median OS was 19.2 in the intervention group, compared with 13.4 in the control group. This resulted in a HR of 0.66 (95% CI 0.53 to 0.81). This difference is considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'overall survival' is considered *low.*

Lenvatinib versus Sorafenib
Kudo (2018) reported OS, which measured from the date of randomization until the date of death from any cause. The median OS was 13.6 in the intervention group, compared with 12.3 in the control group. This resulted in a HR of 0.92 (95% CI 0.79 to 1.06). This difference is not considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'overall survival' is considered *low.*

Progression-free survival (PFS) (crucial)
Sorafenib versus placebo
Cheng (2009) reported the time to progression. The median time to progression was 2.8 months in the intervention group, compared with 1.4 months in the control group. This resulted in a HR of 0.57 (95% CI 0.42 to 0.79). This difference is considered clinically relevant.

Llovet (2008) reported the time to symptomatic progression. The median time to symptomatic progression was 4.1 months in the intervention group, compared with 4.9 in the control group. This resulted in a HR of 0.58 (95% CI 0.45 to 0.74). This difference is considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the studies were RCTS. The level of evidence was downgraded by 3 levels, because of study limitations (risk of bias, -1 (see RoB assessment)) and low number of patients (imprecision, -1), differences in outcome measures (indirectness, -1). Therefore, the level of evidence for the outcome 'progression-free survival' is considered *very low.*

Atezolizumab + Bevacizumab versus Sorafenib
Cheng (2022) reported PFS. The median PFS was 6.9 in the intervention group, compared with 4.3 in the control group. This resulted in a HR of 0.65 (95% CI 0.53 to 0.81). This difference is considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'progression-free survival' is considered *low.*

Lenvatinib versus Sorafenib
Kudo (2018) reported PFS. The median PFS was 7.3 in the intervention group, compared with 3.6 in the control group. This resulted in a HR of 0.64 (95% CI 0.55 to 0.75. This difference is considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'progression-free survival' is considered *low.*

Tumour response rate (important)
Sorafenib versus placebo
Two studies (Llovet, 2008; Cheng, 2009) reported the response rate.

Llovet (2008) reported the tumour response rate, defined as the proportion of patients with a best response of complete response or partial response according to RECIST. There were no complete responses in either group. In the intervention group 7/299 (2.3%) achieved a partial response, compared with 2/303 (0.7%) in the control group. The RD was 1.7% (95% CI -0.26 to 3.6). This difference is not considered clinically relevant.

Cheng (2009) reported the tumour response, defined as the proportion of patients with a best response of complete response or partial response according to RECIST. There were no complete responses in either group. In the intervention group 5/150 (3.3%) achieved a partial response, compared with 1/76 (1.3%) in the control group. The RD was 2% (95% CI -1.8 to 5.9). This difference is not considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the studies were RCTS. The level of evidence was downgraded by 3 levels, because of study limitations (risk of bias, -1 (see RoB assessment)) and low number of events (imprecision, -2). Therefore, the level of evidence for the outcome 'tumour response rate' is considered *very low.*

Atezolizumab + Bevacizumab versus Sorafenib
Cheng (2022) reported the tumour response, defined as the proportion of patients with a best response of complete response or partial response according to RECIST 1.1. In the intervention group, 25/326 (7.7%) patients achieved a complete response and 72/326 (22.1%) a partial response.

In the control group 1/159 (0.6%) patients achieved a complete response and 17/159 (10.7%) a partial response. The overall response rate was 97/326 (29.8%) in the intervention group compared to 18/159 (11.3%) in the control group. The RD was 18.4% (95% CI 11.4 to 25.4). This difference is not considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'tumour response rate' is considered *low.*

Lenvatinib versus Sorafenib
Kudo (2018) reported the tumour response, defined as the proportion of patients with a best response of complete response or partial response according to a masked independent imaging review with a modified RECIST (mRECIST). In the intervention group, 10/478 (2.1%) patients achieved a complete response and 184/478 (38.5%) a partial response. In the control group 4/476 (0.8%) patients achieved a complete response and 55/476 (11.6%) a partial response. The overall response rate was 194/478 (40.6%) in the intervention group, compared to 59/476 (12.4%) in the control group. The RD was 28.2% (95% CI 22.9 to 33.5). This difference is considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'tumour response rate' is considered *low.*

Serious adverse events (important)
Sorafenib versus placebo
Two studies (Llovet, 2008; Cheng, 2009) reported the incidence of serious treatment-emergent adverse events.

Llovet (2008) reported the incidence of serious treatment-emergent adverse events.

In the intervention group was 52/297 (17.5%) patients experienced a treatment-emergent adverse event, compared with 54/302 (17.9%) in the control group. Diarrhea, weight loss, hand–foot skin reaction, and hypophosphatemia were more frequent in the sorafenib group (intervention). The RD was -0.4% (95% CI -6.5 to 5.8). This difference is not considered clinically relevant.

Cheng (2008) reported the incidence of serious treatment-emergent adverse events. In the intervention group, 71/149 (47.7%) patients experienced a treatment-emergent adverse event, compared with 34/75 (45.3%) in the control group. Hand-foot skin reactions, diarrhoea and fatigue were more frequent in the sorafenib group (intervention). The RD was 2.3% (95% CI -11.5 to 16.1). This difference is not considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the studies were RCTS. The level of evidence was downgraded by 3 levels, because of study limitations (risk of bias, -1 (see RoB assessment)) and low number of events (imprecision, -2). Therefore, the level of evidence for the outcome 'serious adverse events' is considered *very low.*

Atezolizumab + Bevacizumab versus Sorafenib
Cheng (2022) reported the incidence of serious adverse events and the incidence of serious treatment-emergent adverse events. In the intervention group, 76/329 (23.1%) patients experienced a treatment-emergent adverse event, compared with 25/156 (16.0%) in the control group.

Proteinuria, hypertension and fatigue was most comment with atezolizumab plus bevacizumab (intervention), whereas palmar-plantar, erythrodysesthesia syndrome and diarrhea was most common in the sorafenib arm (control). The RD was 7.1% (95% CI -0.27 to 14.4). This difference is not considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'serious adverse events' is considered *low.*

Lenvatinib versus Sorafenib
Kudo (2018) reported the incidence of serious treatment-emergent adverse events. In the intervention group, 205/476 (43.1%) patients experienced a treatment-emergent adverse event, compared with 144/475 (30.3%) in the control group. Hypertension, diarrhea, decreased appetite, and decreased weight was most common in the lenvatinib arm (intervention), whereas palmar-plantar erythrodysaesthesia, diarrhoea, hypertension, and decreased appetite was most common in the sorafenib arm (control). The RD was 12.8% (95% CI 6.7 to 18.8). This difference is not considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'serious adverse events' is considered *low.*

Quality of life (important)
Sorafenib versus placebo
Quality of life was not reported.

Level of evidence of the literature
The level of evidence was not graded because no study reported quality of life.

Atezolizumab + Bevacizumab versus Sorafenib
Finn (2020) reported on the patient-reported outcomes, which were evaluated with the use of the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire for cancer (EORTC QLQ–C30). Finn (2020) reported the time to deterioration of quality of life, which was defined as decrease from baseline of 10 or more point on the EORTC QLQ–C30 maintained for two consecutive assessments or a decrease of 10 points or more in one assessment followed by death from any cause within 3 weeks. The median time to deterioration of patient-reported quality of life in the intervention group was 11.2 months (95% CI, 6.0 to not estimable), compared to 3.6 months (95% CI, 3.0 to 7.0) (HR 0.73, 95% CI 0.46 to 0.85) (favours atezolizumab + bevacizumab). This difference is considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'quality of life' is considered *low.*

Lenvatinib versus Sorafenib
Kudo (2018) reported the quality of life, which was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)23,24 and the hepatocellular carcinoma-specific EORTC QLQ-HCC1825 health questionnaires. For between-group comparison, the summary score was not significantly different between the treatment arms (HR

0.87, 95% CI 0.75 to 1.01)(QLQ-C30 questionnaire). HCC18 questionnaire domains ranges between 0.79 (body image, favours lenvatinib) and 1.14 (pain, favours sorafenib). This difference is not considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'quality of life' is considered *low.*

Second-line treatment
Overall survival (OS) (crucial)
Regorafenib versus placebo
Bruix (2017) reported the median OS, which was measured from the date of randomization until the date of death from any cause. The median OS was 10.6 months in the intervention group, compared with 7.6 in de control group. This resulted in a HR of 0.63 (95% CI 0.50 to 0.79). This difference is considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'overall survival' is considered *low.*

Progression-free survival (PFS) (crucial)
Regorafenib versus placebo
Bruix (2017) reported the median PFS. The median PFS was 3.4 months in the intervention group, compared with 1.5 in de control group. This resulted in a HR of 0.43 (95% CI 0.35 to 0.52). This difference is considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'progression-free survival' is considered *low.*

Tumour response rate (important)
Regorafenib versus placebo
Bruix (2017) reported the objective response rate. In the intervention group, 2/379 (0.5%) patients achieved a complete response and 38/379 (10.0%) a partial response. In the control group 0/194 (0%) patients achieved a complete response and 8/194 (4.1%) a partial response. The overall response rate was 40/379 (10.6%) in the intervention group, compared to 8/194 (4.1%) in the control group. The RD was 6.4% (95% CI 2.3 to 10.6). This difference is not considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'tumour response rate' is considered *low.*

Serious adverse events (important)
Regorafenib versus placebo
Bruix (2017) reported the incidence of serious adverse events.

In the intervention group was 166/397 (41.8%) patients experienced a serious adverse event, compared with 90/194 (46.3%) in the control group. Diarrhea, weight loss, hand–foot skin reaction,

and hypophosphatemia were more frequent in the sorafenib group (intervention). Hypertension, hand-foot skin reaction, fatigue, and diarrhea were more frequent in the regorafenib group (intervention). The RD was -2.6% (95% CI -11.2 to 6.0). This difference is not considered clinically relevant.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'serious adverse events' is considered *low.*

Quality of life
Regorafenib versus placebo
Quality of life was assessed with the Functional Assessment of Cancer Therapy (FACT-G), FACT-Hepatobiliary (FACT-Hep), EQ-5D and EQ-VAS. No clinically meaningful differences were noted between the regorafenib and placebo groups in HRQoL.

Level of evidence of the literature
The level of evidence started as high, because the study was an RCT. The level of evidence was downgraded by 2 levels, because the optimal information size criteria is not met (imprecision, -2). Therefore, the level of evidence for the outcome 'quality of life' is considered *low.*

First-line treatment
Conclusions
Overall survival (crucial)
Sorafenib versus placebo

Low GRADE	Treatment with sorafenib may result in a higher **overall survival** when compared with placebo in patients with hepatocellular carcinoma. *Sources: (Llovet, 2008; Cheng, 2009)*

Atezolizumab + Bevacizumab versus Sorafenib

Low GRADE	Treatment with atezolizumab + bevacizumab may result in a higher **overall survival** when compared with sorafenib in patients with hepatocellular carcinoma. *Sources: (Cheng, 2022)*

Lenvatinib versus Sorafenib

Low GRADE	Treatment with lenvatinib may result in little to no difference in **overall survival** when compared with sorafenib in patients with hepatocellular carcinoma. *Sources: (Kudo, 2018)*

Progression-free survival (crucial)
Sorafenib versus placebo

Very low GRADE	The evidence is very uncertain about the effect of sorafenib on **progression-free survival** when compared with placebo in patients with hepatocellular carcinoma. *Sources: (Llovet, 2008; Cheng, 2009)*

Atezolizumab + Bevacizumab versus Sorafenib

Low GRADE	Treatment with atezolizumab + bevacizumab may result in higher **progression-free survival** when compared with sorafenib in patients with hepatocellular carcinoma. *Sourcse: (Cheng, 2022)*

Lenvatinib versus Sorafenib

Low GRADE	Treatment with lenvatinib may result in a higher **progression-free survival** when compared with sorafenib in patients with hepatocellular carcinoma. *Sources: (Kudo, 2018)*

Tumour response rate (important)

Sorafenib versus placebo

Very Low GRADE	The evidence is very uncertain about the effect of sorafenib on **tumour response rate** when compared to placebo in patients with hepatocellular carcinoma. *Sources: (Llovet, 2008; Cheng, 2009)*

Atezolizumab + Bevacizumab versus Sorafenib

Low GRADE	Treatment with atezolizumab + bevacizumab may result in a higher **tumour response rate** when compared with sorafenib in patients with hepatocellular carcinoma. *Sources: (Cheng, 2022)*

Lenvatinib versus Sorafenib

Low GRADE	Treatment with lenvatinib may result in a higher **tumour response rate** when compared with sorafenib in patients with hepatocellular carcinoma. *Sources: (Kudo, 2018)*

<u>Serious adverse events (important)</u>

Sorafenib versus placebo

Very Low GRADE	The evidence is very uncertain about the effect of sorafenib on **serious adverse events** when compared to placebo in patients with hepatocellular carcinoma. *Sources: (Llovet, 2008; Cheng, 2009)*

Atezolizumab + Bevacizumab versus Sorafenib

Low GRADE	Treatment with atezolizumab + bevacizumab may result in little to no difference in **serious adverse events** when compared with sorafenib in patients with hepatocellular carcinoma. *Sources: (Cheng, 2022)*

Lenvatinib versus Sorafenib

Low GRADE	Treatment with lenvatinib may result in little to no difference in **serious adverse events** when compared with sorafenib in patients with hepatocellular carcinoma. *Sources: (Kudo, 2018)*

Quality of life (important)

Sorafenib versus placebo

- grade	No evidence was found regarding the effect of sorafenib on the **quality of life** when compared with placebo in in patients with hepatocellular carcinoma.

Atezolizumab + Bevacizumab versus Sorafenib

Low GRADE	Treatment with atezolizumab + bevacizumab may result in a higher **quality of life** when compared with sorafenib in patients with hepatocellular carcinoma. *Sources: (Finn, 2020)*

Lenvatinib versus Sorafenib

Low GRADE	Treatment with lenvatinib may result in little to no difference in **quality of life** when compared with sorafenib in patients with hepatocellular carcinoma. *Sources: (Kudo, 2018)*

Second-line treatment

Conclusions

Overall survival (crucial)

Regorafenib versus placebo

Low GRADE	Treatment with regorafenib may result in a higher **overall survival** when compared with placebo in patients with hepatocellular carcinoma. *Sources: (Bruix, 2017)*

Progression-free survival (crucial)

Regorafenib versus placebo

Low GRADE	Treatment with regorafenib may result in a higher **progression-free survival** when compared with placebo in patients with hepatocellular carcinoma. *Sources: (Bruix, 2017)*

Tumour response rate (important)

Regorafenib versus placebo

Low GRADE	Treatment with regorafenib may result in little to no difference in **tumour response rate** when compared with placebo in patients with hepatocellular carcinoma. *Sources: (Bruix, 2017)*

Serious adverse events (important)
Regorafenib versus placebo

Low GRADE	Treatment with regorafenib may result in little to no difference in **serious adverse events** when compared with placebo in patients with hepatocellular carcinoma. *Sources: (Bruix, 2017)*

Quality of life (important)
Regorafenib versus placebo

Low GRADE	Treatment with regorafenib may result in little to no difference in **quality of life** when compared with placebo in patients with hepatocellular carcinoma. *Sources: (Bruix, 2017)*

Third-line treatment

Conclusions

Overall survival (crucial), progression-free survival (crucial), tumour response rate (important), serious adverse events (important), quality of life (important)

- GRADE	No evidence was found in the third-line treatment setting for patients with hepatocellular carcinoma.

Overwegingen – van bewijs naar aanbeveling

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

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen de verschillende (eerste, tweede en derdelijns) behandelingen die in Nederland aangeboden worden. Tot en met 15 april 2022 werden er vier gerandomiseerde gecontroleerde studies (RCTs) gevonden in de eerstelijnsbehandeling en één studie in de tweedelijnsbehandeling. Er zijn geen studies gevonden naar een derdelijns behandeling bij gevorderd of gemetastaseerd hepatocellulair carcinoom. Na de zoekdatum is er een update beschikbaar gekomen van één van de geïncludeerde RCTs. Deze is ook meegenomen in de literatuuranalyse (Cheng, 2022).

Binnen de eerstelijnsbehandeling werden vier RCTs gevonden, waarbij sorafenib vergeleken werd met placebo (Llovet, 2008; Cheng, 2009), lenvatinib met sorafenib (Kudo, 2018) en atezolizumab + bevacizumab met sorafenib (Finn, 2020; Cheng, 2022). De systematische literatuuranalyse laat zien dat de behandeling met sorafenib vergeleken met placebo een positief effect zou kunnen hebben op de algemene overleving, evenals de behandeling van atezolizumab + bevacizumab vergeleken met sorafenib. Lenvantib is non inferieur aan sorafenib. De overall bewijskracht van de literatuur binnen de eerstelijnsbehandelingen werd gegradeerd als laag en zeer laag. Dit heeft te maken met de imprecisie van de bevindingen (kleine aantal studies) en beperkingen in studie opzet (risk of bias).

Voor de tweedelijns behandeling werd één RCT gevonden, waarbij regorafenib vergeleken werd met placebo (Bruix, 2017). De systematische literatuuranalyse laat zien dat de behandeling met regorafenib positieve effecten zou kunnen hebben op de totale en ziektevrije overleving. Voor de uitkomstmaten tumor respons, complicaties en kwaliteit van leven waren er geen positieve klinische effecten te zien. De overall bewijskracht van de literatuur binnen de tweedelijnsbehandelingen werd gegradeerd als laag. Dit heeft te maken met imprecisie van de bevindingen doordat de bevindingen gebaseerd zijn op één studie. De Celestial studie is niet geselecteerd omdat patiënten met tweedelijns en derdelijns palliatieve systeemtherapie geïncludeerd werden, zonder dat hiervoor gestratificeerd werd. De overlevingswinst van deze groepen samen waren wel statistisch significant

maar voldeden niet aan de PASKWIL criteria (OS van 10,2 versus 8,0 maanden; Δ 2,2 maanden, HR: 0,76; 95%-BI: 0,63- tot 0,92; P = 0,005).

Al de geïncludeerde fase III studies bevatten patiënten met Child-Pugh A (behalve Cheng, 2009) waardoor er geen uitspraak te doen is over patiënten met een Child-Pugh B leverrcirose. Op basis van retrospectieve data is terughoudendheid geboden voor behandeling met palliatieve systeemtherapie bij de groep met Child–Pugh B (Labeur, 2018) omdat deze data tonen dat de effectiviteit van de systeemtherapie minder is dan in de originele studie gezien werd. Tevens geldt dat terughoudendheid in acht moet worden genomen bij een geconjugeerd bilirubine van 3 keer ULN omdat dat in de meeste studies een exclusiecriterium was

Overige overwegingen
Waarden en voorkeuren van patiënten (en eventuele hun verzorgers)
Indien er een mogelijkheid is voor palliatieve systeemtherapie of best supportive care, is het wenselijk om de beslissing samen met de patiënt te nemen. Doel van palliatieve systeemtherapie is verlenging van overleving en vergroting van kwaliteit van leven. Persoonlijke voorkeuren van de patiënt zijn van grote invloed op deze keuze om wel of niet palliatieve systeemtherapie te starten.

In geval van wens voor palliatieve systeemtherapie heeft in eerstelijn atezolizumab met bevacizumab een grotere winst op OS (19.2 maanden versus 13.4 maanden, HR 0.66) en op kwaliteit van leven in vergelijking met sorafenib. De mediane tijd tot verslechtering van kwaliteit van leven was 11.2 maanden met atezolizumab plus bevacizumab versus 3.6 maanden met sorafenib (HR 0.73 95% CI 0.46 tot 0.85). Behandelgerelateerde bijwerkingen graad 3/4 waren gelijk namelijk 43 % in de groep met atezolizumab en bevacizumab versus 46% met sorafenib. Aspecten die gecontroleerd dienen te worden zijn of er contra-indicaties zijn voor immuuntherapie en of er therapeutische antistolling gebruikt wordt. In beide gevallen is behandeling met atezolizumab plus bevacizumab relatief gecontra-indiceerd. Daarnaast moet de leverfunctie voldoende zijn en dienen oesophagusvarices behandeld te zijn, indien geïndiceerd.

Indien er een contra-indicatie voor atezolizumab en/of bevacizumab is, heeft de behandelend arts in samenspraak met de patiënt de keuze om te starten met sorafenib of lenvatinib. Vanwege de langere ervaring met sorafenib versus lenvantinib en de lagere kosten heeft sorafenib de voorkeur boven lenvatinib. Echter, indien een snelle respons gewenst is, is lenvatinib te prefereren boven sorafenib (ORR lenvantinib 40.6% vergeleken met 12.4% met sorafenib). Behandelgerelateerde graad 3-4 bijwerkingen van sorafenib versus lenvatinib waren vergelijkbaar, maar het bijwerkingen patroon was verschillend. Dus bij toxiciteit van sorafenib kan een switch gemaakt worden naar lenvantinib.

De tweedelijns studie met regorafenib versus placebo toont een bescheiden overlevingswinst en geen verschil in kwaliteit van leven in vergelijking met placebo. Overweeg deze behandeling alleen bij fitte patiënten die progressief zijn onder behandeling met sorafenib en een goede leverfunctie hebben.

Er is nog geen wetenschappelijk bewijs voor tweedelijns behandeling na atezolizumab en bevacizumab. In dit geval zal op basis van klinische expertise, bijwerkingen profiel een afweging voor sorafenib conform de add-on gemaakt worden.

Op basis van exploratieve analyses zijn in zijn algemeenheid enkele prognostisch slechte factoren te duiden, te weten aanwezigheid van macrovasculaire invasie en een hoog alpha FP.

Bij patiënten met een fibrolamellair HCC zal casus per casus overwogen moet worden welke behandeling het best toepasbaar is, omdat deze patiënten bij elke interventiestudie met HCC geëxcludeerd werden.

Kosten (middelenbeslag)
Er zijn geen studies verricht naar kosteneffectiviteit van atezolizumab en bevacizumab versus sorafenib. De kosten van atezolizumab zijn substantieel hoger dan die van sorafenib. Echter, omdat de effectiviteit van atezolizumab en bevacizumab zo duidelijk groter is, spelen de kosten een ondergeschikte rol bij de afweging.

Aanvaardbaarheid, haalbaarheid en implementatie
Bij voorkeur behandelen in gespecialiseerd centrum waar multidisciplinaire kennis is van het HCC conform SONCOS-normeringen.

Aanbeveling
Aanbeveling (1)
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Persoonlijke voorkeuren van de patiënt zijn van grote invloed op deze keuze om wel of niet palliatieve systeemtherapie te starten, zeker gezien de verwachte winst in overleving versus de kwaliteit van leven. Daarom is de aanbeveling zo geformuleerd dat altijd in overleg met de patiënt wordt besloten of er wel of niet met palliatieve systeemtherapie wordt gestart.

Maak samen met de patiënt een afweging om wel of geen palliatieve systeemtherapie te starten. Bespreek de wensen en verwachtingen van de patiënt.

Bepaal voorafgaand aan de behandeling de leverfunctie. Een voldoende behouden leverfunctie is een voorwaarde om te starten met systeemtherapie (waarbij terughoudendheid bij een hoog geconjugeerd biluribine wordt geadviseerd).

Geef bij patiënten met een behouden leverfunctie, die met eerstelijns palliatieve systeemtherapie behandeld willen worden, atezolizumab plus bevacizumab. Verifieer voor start dat er een gastroscopie is die niet ouder is dan 6 maanden met behandelde varices alvorens de behandeling te starten.

Geef sorafenib of lenvatinib bij patiënten die met palliatieve systeemtherapie behandeld willen worden die een behouden leverfunctie hebben, maar een contra-indicatie voor atezolizumab en bevacizumab. Hierbij heeft sorafenib de voorkeur gezien uitgebreidere ervaring en kosten, behoudens bij patiënten waarbij snelle respons noodzakelijk is, dan heeft lenvatinib de voorkeur.

Overweeg sorafenib in tweedelijn bij progressie op atezolizumab plus bevacizumab,.

Overweeg regorafenib in de volgende lijn bij progressie op sorafenib.

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Bijlagen bij module 6

Table of excluded studies

Author and year	Reason for exclusion
Ahmed 2021	Study by Finn (2020) is already Included in Park (2021). The study from Lee (2020 is a phase 1b study and compares the treatment atezolizumab with or without bevacizumab in unresectable HCC (not of interest).
An 2021	The RCTs that studied the comparisons of interests are already included in the selected SR.
Chen 2021	The RCTs that studied the comparisons of interests are already included in the selected SR.
Facciorusso 2021	The RCTs that studied the comparisons of interests are already included in the selected SR.
Jácome 2021	The RCTs that studied the comparisons of interests are already included in the selected SR.
Kudo 2021	Pooled results from REACH and REACH-2 studies. Comparison not of interest.
Liu 2021	The RCTs that studied the comparisons of interests are already included in the selected SR.
Rizzo 2022	Background article
Ronnebaum 2022	The RCTs that studied the comparisons of interests are already included in the selected SR.
Vogel 2021	The RCTs that studied the comparisons of interests are already included in the selected SR.
Ziogas 2021	The RCTs that studied the comparisons of interests are already included in the selected SR.

Evidence tables

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
First-line treatments							
Atezolizumab + Bevacizumab versus Sorafenib							
Finn, 2020 (IMbrave150) NCT03434379	Type of study: Randomized, open-label, phase 3 trial Setting and country: The study was conducted at 111 sites in 17 countries (Australia, China, Czech Republic, France, Germany, Hong Kong, Italy, Japan, Republic of Korea, Poland, Russia, Singapore, Spain, Taiwan, UK, US) Patients were enrolled between March 13, 2018, and January 30, 2019 Funding and conflicts of interest: F. Hoffmann-La Roche/Genentech Conflicts of interest are disclosed	Patients with unresectable HCC who had not received previous systemic treatment <u>Inclusion criteria</u>: • ≤18 years of age • Locally advanced metastatic or unresectable HCC (or both) • No previous systematic therapy • ECOG score 0 or 1 • Child-Pugh A <u>Exclusion criteria</u>: • History of autoimmune disease • Coinfection with hepatitis B or C • Untreated or incompletely treated esophageal or gastric varices with bleeding or high risk of bleeding. <u>N total at baseline</u>: N = 573 Intervention: N=336 Control: N=165	Atezolizumab + Bevacizumab Participants received Atezolizumab + Bevacizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator Drug: Atezolizumab was administered by IV, 1200 mg on day 1 of each 21 day cycle Drug: Bevacizumab was administered by IV, 15 mg/kg on day 1 of each 21 day cycle	Sorafenib Participants received Sorafenib until unacceptable toxicity or loss of clinical benefit as determined by the investigator Drug: Sorafenib Sorafenib was administered by mouth, 400 mg twice per day, on days 1-21 of each 21-day cycle	<u>Length of follow-up</u>: Median follow-up I: 8.6 months C: 8.1 months <u>Loss-to-follow-up & incomplete outcome data:</u> Intervention: N=7/336 (2.1%) did not receive assigned treatment Control: N=9/165 (N=5.5%) did not receive assigned treatment Intervention: N=108/336 (32.1%) discontinued the trial Reasons: N=95/336 (28.3%) died	<u>Overall survival</u> Median OS (months) I: Could not be evaluated (NE) C: 13.2 (10.4 – NE) HR: 0.58 (95% CI, 0.42 to 0.79) <u>Progression-free survival</u> Median PFS (months) I: 6.8 (95% CI, 5.7 to 8.3) C: 4.3 (95% CI 4.0 to 5.6) HR for disease progression or death HR: 0.59 (95% CI, 0.47 to 0.76) <u>Objective response (RECIST 1.1)</u> Complete response I: 18/326 (5.5%) C: - Partial response	• Child-Pugh class A patient population • See Cheng 2022 <u>Authors conclusion:</u> *" In conclusion, treatment with atezolizumab plus bevacizumab was associated with significantly better overall survival and progression-free survival outcomes than sorafenib in patients with advanced unresectable hepatocellular carcinoma not previously treated with systemic therapy. Serious toxic effects were noted in 38% of the patients who received the combination therapy; however, no new or unexpected toxic effects were observed. The combination therapy also resulted in a longer time to deterioration of patient-reported quality of life and functioning than sorafenib."*

		<u>Important prognostic factors</u>: Age, median (range): I: 64 (56-74) C: 66 (59-71) Sex, n/N (%) male: I: 277/336 (82%) C: 137/165 (83%) Groups comparable at baseline? Yes.			N= 1/336 (0.3%) experienced disease progression per RECIST 1.1 N=12/336 (3.6%) withdrew consent Control : 84/165 (50.1%) discontinued the trial Reasons: N=65/165 (39.4%) died N=19/165 (11.5%) withdrew consent	I: 71/326 (21.8%) C: 19/159 (11.9%) <u>Adverse events</u> *From any cause* Grade 3 or 4 I: 186/329 (56.5%) C: 86/156 (55.1%) Grade 5 I: 15/329 (4.6%) C: 9/156 (5.8%) *A detailed record of all adverse events is reported in the article.* <u>Quality of life</u> *Measured with the EORTC QLQ-C30. Reported as time to deterioration of Quality of Life* Median time to deterioration I: 11.2 (CI: 6.0-NE) C: 3.6 (3.0-7.0) HR: 0.73 (95% CI, 0.46-0.85)	
Cheng, 2022 (IMbrave150) NCT03434379	*Updated efficacy and safety data from IMbrave150* *See 'Finn 2020'*	*See 'Finn 2020'*	*See 'Finn 2020'*	*See 'Finn 2020'*	<u>Length of follow-up</u>: Median (range) 15.6 (0-28.6)	<u>Overall survival</u> Median OS (months) I: 19.2 (17.0-23.7) C: 13.4 (11.4-16.9) HR: 0.66 (95% CI, 0.52 to 0.85)	<u>Authors conclusion:</u> *"In conclusion, the updated analysis showed that the safety and tolerability profile of atezolizumab plus bevacizumab remained consistent after longer follow-up. After an additional 12 months of*

						<u>Progression-free survival</u> Median PFS (months) I: 6.9 (95% CI, 5.7 to 8.6) C: 4.3 (95% CI 4.0 to 5.6) HR: 0.65 (95% CI, 0.53 to 0.81) <u>Objective response (RECIST 1.1)</u> Complete response I: 25/326 (7.7%) C: 1/159 (0.6%) Partial response I: 72/326 (22.1%) C: 17/159 (10.7%) Objective response I: 97/326 (30%) C: 18/159 (11%) <u>Adverse events</u> Treatment-related AE Grade 3/4 I: 143/329 (43%) C: 72/156 (46%) Grade 5 I: 6/329 (2%) C: 1/156 (0.6%) <u>Quality of life</u> *Not reported*	*follow-up, the clinically meaningful survival and efficacy benefits of atezolizumab plus bevacizumab over sorafenib were maintained and consistent with the primary analysis. This updated analysis demonstrated the longest median OS observed to date in a first-line phase III study in hepatocellular carcinoma, confirming this treatment combination as the standard of care for systemic treatment-naive unresectable hepatocellular carcinoma."*

Sorafenib versus Placebo							
Llovet, 2008 (SHARP) NCT00105443	Type of study: Randomized, double-blind, placebo-controlled, phase 3 trial Setting and country: The study was conducted at 121 sites in 21 countries in Europe, North America, South America, and Australasia Patients were enrolled between March 10, 2005 and April 11, 2006 Funding and conflicts of interest: Bayer HealthCare Pharmaceuticals-Onyx Pharmaceuticals Conflicts of interest are disclosed	Patients with advanced HCC who had not received previous systemic treatment <u>Inclusion criteria</u>: • ≤18 years of age • No previous systematic therapy • Life expectance of at least 12 weeks • ECOG score 2 or less • Child-Pugh A <u>Exclusion criteria</u>: • Previously received molecularly targeted therapies or any other systemic treatment <u>N total at baseline</u>: N = 602 Intervention: N=299 Control: N=303 <u>Important prognostic factors</u>: Age, mean (SD): I: 64.9 (11.2) C: 66.3 (10.2) Sex, n/N (%) male: I: 260/299 (87%) C: 264/303 (87%) Groups comparable at baseline? Yes.	Sorafenib Sorafenib 400 mg was administered orally at a dose of 400 mg (2 x 200 mg tablets) twice daily; 2 dose reductions to predefined levels of 400 mg once daily (OD) and 400 mg every other day were permitted for adverse events related to study treatment.	Placebo Sorafenib-matching placebo tablets were orally administered twice daily (bid). Follow-up / Open Label phase: Subjects on placebo who chose to switch to sorafenib, received an oral dose of 400 mg (2 x 200 mg tablets) bid; similar to the double-blind study.	<u>Length of follow-up</u>: No information <u>Loss-to-follow-up & incomplete outcome data:</u> Intervention: N=2/299 (0.7%) did not receive assigned treatment Control: N=1/303 (N=0.3%) did not receive assigned treatment Intervention: N=226/299 (75.6%) discontinued the trial Reasons: N=81/299 (35.3%) had an adverse event N=61/299 (20.0%) had radiologic and symptomatic progression	<u>Overall survival</u> Median OS (months) I: 10.7 (9.4-13.2) C: 7.9 (6.8-9.1) HR: 0.69 (95% CI, 0.55 to 0.87) <u>Progression-free survival</u> *Not reported* Time to symptomatic progression Median (months) I: 4.1 (3.5-4.8) C: 4.9 (4.2-6.3) HR: 0.58 (0.45 to 0.74) <u>Objective response (RECIST)</u> Complete I: 0/299 (0%) C: 0/303 (0%) Partial I: 7/299 (2.3%) C: 2/303 (0.7%) Numbers in tables and text are inconsistent <u>Adverse events</u> Treatment-emergent adverse events	• Child-Pugh class A patient population <u>Authors conclusion:</u> • *"In patients with advanced hepatocellular carcinoma, median survival and the time to radiologic progression were nearly 3 months longer for patients treated with sorafenib than for those given placebo."*

					N=28/299 (9.4%) withdrew consent N=3/299 (1%) died N=1/299 (0.3%) had ECOG score of 4 N=47/299 (15.7%) had other reasons Control: N=242/303 (79.9%) discontinued the trial Reasons: N=90/303 (29.7%) had an adverse event N=62/303 (20.4%) had radiologic and symptomatic progression N=25/303 (8.3%) withdrew consent N=7/303 (2.3%) had ECOG score of 4 N=6/303 (2.0%) died	Grade 3: I: 39/297 (13.1%) C: 24/302 (7.9%) Grade 4: I: 6/297 (2.0%) C: 8/302 (2.6%) Serious treatment-emergent adverse events I: 52/297 (17.5%) C: 54/302 (17.9%) *Data was provided in percentages per adverse event. A detailed record of all adverse events is reported in the article.* <u>Quality of life</u> *Not reported*	

					N=52/303 (17.2%) had other reasons		
Cheng, 2009 NCT00492752	Type of study: Randomized, double-blind, placebo-controlled, phase 3 trial Setting and country: The study was conducted at 23 sites in China, South Korea and Taiwan Patients were enrolled between September 20, 2005 and January 31, 2007 Funding and conflicts of interest: Bayer HealthCare Pharmaceuticals-Onyx Pharmaceuticals Conflicts of interest are disclosed	Patients with advanced HCC who had not received previous systemic treatment <u>Inclusion criteria</u>: • ≤18 years of age • No previous systematic therapy • Life expectance of at least 12 weeks • ECOG score 2 or less • Child-Pugh A <u>Exclusion criteria</u>: • Previously received molecularly targeted therapies or any other systemic treatment <u>N total at baseline</u>: N = 226 Intervention: N=150 Control: N=76 <u>Important prognostic factors</u>: Age, median (range): I: 51 (23-86) C: 52 (25-79) Sex, n/N (%) male: I: 127/150 (84.7%) C: 66/76 (86.8%)	Sorafenib Sorafenib 400 mg was administered orally at a dose of 400 mg (2 x 200 mg tablets) twice daily; 2 dose reductions to predefined levels of 400 mg once daily (OD) and 400 mg every other day were permitted for adverse events related to study treatment	Placebo Placebo tablets matching in appearance were orally administered bid (twice daily)	<u>Length of follow-up</u>: No information <u>Loss-to-follow-up & incomplete outcome data:</u> Intervention: N=129/150 (86%) discontinued treatment Control: N=72/75 (N=96%) discontinued treatment Intervention: Reasons: N=69/150 (46%) had disease progression N=22/150 (14.7%) adverse events N=23/150 (15.3%) withdrew consent	<u>Overall survival</u> Median OS (months) I: 6.5 (5.56-7.56) C: 4.2 (3.75-5.46) HR: 0.68 (95% CI, 0.50 to 0.93) <u>Progression-free survival</u> *Not reported* Median time to progression (months) I: 2.8 (2.63-3.58) C: 1.4 (1.35-1.55) HR: 0.57 (0.42 to 0.79) <u>Objective response (RECIST)</u> Complete I: 0/150 (0%) C: 0/150 (0%) Partial I: 5/150 (3.3%) C: 1/76 (1.3%) <u>Adverse events</u> Treatment-emergent serious adverse event I: 71/149 (47.7%)	• Child-Pugh class A patient population <u>Authors conclusion:</u> • *"Our study shows that sorafenib is a well-tolerated treatment option with an acceptable safety profile for patients with advanced hepatocellular carcinoma from the Asia-Pacific region. The efficacy results of our study were consistent with those of the SHARP trial, despite the patients randomised in our study having more advanced disease and being more likely to have different disease aetiologies (eg, HBV infection) than the patients randomised in the SHARP trial. Furthermore, the primary findings and subanalyses of our study suggest that sorafenib could be used to treat patients with hepatocellular carcinoma with different prognostic factors."*

		Groups comparable at baseline? Yes.			N=12/150 (8%) died N=2/150 (1.3%) lost to follow-up N=1/150 (0.7%) non-compliant to treatment Control Reasons: N=48/76 (63.2%) had disease progression N=7/76 (9.2%) adverse events N=11/76 (14.5%) withdrew consent N=2/76 (2.6%) died N=3/76 (3.9%) lost to follow-up N=1/76 (1.3%) protocol violation	C: 34/75 (45.3%) Drug-related serious adverse events of any grade I: 122/149 (81.9%) C: 29/75 (38.7%) *Data was provided in percentages per adverse event. A detailed record of all adverse events is reported in the article.* <u>Quality of life</u> *Not reported*	
Levatinib versus Sorafenib							
Kudo, 2018 NCT01761266	Type of study: Randomized, double-blind, placebo-controlled, phase 3 trial Setting and country:	Patients with unresectable HCC <u>Inclusion criteria</u>: • ≤18 years of age • No previous systematic therapy	Lenvatinib Participants received lenvatinib capsules 12 milligram (mg) based on the participant's body weight greater than or	Sorafenib Participants received sorafenib 400 mg tablets, orally, twice daily (BID) in continuous	<u>Length of follow-up</u>: Median (months) I: 27.4 (95% CI, 26.4-29.3)	<u>Overall survival</u> Median OS (months) I: 13.6 (12.1-14.9) C: 12.3 (10.4-13.9) HR: 0.92 (95% CI, 0.79 to 1.06)	• Child-Pugh class A patient population <u>Authors conclusion:</u> • *"In conclusion, this study showed non-inferiority of*

	The study was conducted at 23 sites in China, South Korea and Taiwan Patients were enrolled between September 20, 2005 and January 31, 2007 Funding and conflicts of interest: Eisai Inc Conflicts of interest are disclosed	• Child-Pugh A • Life expectance of at least 12 weeks <u>Exclusion criteria</u>: • 50% or higher liver occupation, obvious invasion of the bile duct, or invasion at the main portal vein • Received previous systemic therapy for HCC <u>N total at baseline</u>: N = 954 Intervention: N=478 Control: N=476 <u>Important prognostic factors</u>: Age, median (range): I: 63.0 (20-88) C: 62.0 (22-88) Sex, n/N (%) male: I: 405/478 (85%) C: 401/476 (84%) Groups comparable at baseline? Yes.	equal to (>=) 60 kilogram (kg) or 8 mg based on the participant's body weight less than (<) 60 kg at baseline, orally, once daily (QD) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, participant request, or withdrawal of consent.	28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, participant request, or withdrawal of consent.	C: 27.1 (95% CI, 25.9-27.7) <u>Loss-to-follow-up & incomplete outcome data:</u> Intervention: N=476/478 (99.6%) received assigned treatment N-475/476 (99.8%) received assigned treatment Intervention: 449/478 (93.9%) discontinued treatment Reasons: N=311/478 (65.1%) radiological progression N=65/478 (13.2%) adverse events N=32/478 (6.7%) clinical progression N=28/478 (5.9%) patient's choice	<u>Progression-free survival</u> Masked independent imaging review according to mRECIST I: 7.3 (5.6-7.5) C: 3.6 (3.6-3.7) HR: 0.64 (95% CI, 0.55-0.75) <u>Objective response (RECIST 1.1)</u> Complete I: 10/478 (2.1%) C: 4/476 (0.8%) Partial I: 184/478 (38.5%) C: 55/476 (11.6%) <u>Adverse events</u> Treatment-related treatment-emergent adverse event of grade ≥3 I: 270/476 (57%) C: 231/475 (49%) *A detailed record of all adverse events is reported in the article.* <u>Quality of life</u> For between-group comparison, the summary score	*lenvatinib versus sorafenib in terms of overall survival, as well as statistically significant and clinically meaningful improvement in progression-free survival, time to progression, and objective response rate. The safety profiles of lenvatinib and sorafenib in our study appear consistent with the known safety profiles of these drugs in hepatocellular carcinoma, and no new safety signals were identified. Based on our results, lenvatinib might be a potential new treatment option for advanced hepatocellular carcinoma."*

					N=3/478 (0.6%) lost to follow-up N=9/478 (1.9%) withdrew consent N=3/478 (0.6%) other Control: 450/476 (94.5%) discontinued treatment Reasons: N=347/476 (72.9%) radiological progression N=43/476 (9.1%) adverse events N=33/476 (7.0%) clinical progression N=14/476 (2.9%) patient's choice N=1/476 (0.2%) lost to follow-up N=5/476 (1.1%) withdrew consent N=7/476 (1.5%) other	was not significantly different between the treatment arms (HR 0.87, 95% CI 0.754–1.013, appendix). (QLQ-C30 questionnaire) HCC18 questionnaire domains ranges between 0.79 (body image, favours Lenvatinib) and 1.14 (pain, favours Sorafenib)	

Second-line treatment							
Regorafenib versus placebo							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Bruix, 2017 (RESORCE) NCT01774344	Type of study: Randomized double-blind, placebo-controlled, phase 3 trial Setting and country: The study was conducted at 152 sites 21 countries in Asia. Funding and conflicts of interest: Bayer Conflicts of interest are disclosed	Patients with HCC who have progressed during sorafenib treatment <u>Inclusion criteria</u>: • Confirmed HCC • Failure to prior treatment with sorafenib • BCLC stage B or C • No benefit from resection, local ablation, or chemoembolization • Child-Pugh A <u>Exclusion criteria</u>: • Received any other previous treatment for HCC or if they discontinued sorafenib for toxicity <u>N total at baseline</u>: N = 573 Intervention: N=379 Control: N=194 <u>Important prognostic factors</u>: Age, median (range): I: 64 (54-71) C: 62 (55-68)	Regorafenib 160 mg orally (p.o.) every day (qd) for 3 weeks of every 4 week cycle (i.e. 3 weeks on, 1 week off) + best supportive care Drug: Regorafenib (Stivarga, BAY73-4506) Regorafenib, 40 mg tablets	Placebo 4 matching placebo tablets for 3 weeks of every 4 week cycle (i.e. 3 weeks on, 1 week off) + best supportive care	<u>Length of follow-up</u>: Not specified <u>Loss-to-follow-up & incomplete outcome data:</u> Intervention: N=5/379 (1.3%) did not receive regorafenib Control: N=1/194 (0.5%) did not receive placebo Intervention: 309/374 (82.6%) discontinued treatment Primary reason: N= 149/374 (39.8%) progressive disease, radiological progression	<u>Overall survival</u> (ITT cohort) Median OS (months) I: 10.6 (95% CI 9.1 to 12.1) C: 7.8 (95% CI 6.3 to 8.8) HR 0.63 (95% CI 0.5 to 0.79) P<0.001 <u>Progression-free survival</u> Median PFS (months) (RECIST 1.1) I: 3.4 (95% CI 2.9 to 4.2) C: 1.5 (95% CI 1.4 to 1.5) HR 0.43 (95% CI 0.35 to 0.52) P<0.001 **numbers are retrieved from the supplementary file and slightly differ from the numbers presented in the article* <u>Objective response</u> I: 40/374 (11%)	• HRQoL was assessed with the Functional Assessment of Cancer Therapy (FACT)–General (FACT-G), FACT–Hepatobiliary (FACT-Hep), EQ-5D, and EQ-VAS questionnaires <u>Authors conclusion:</u> • *"The results of RESORCE show that treatment with regorafenib resulted in a significant improvement in overall survival compared with placebo in patients with disease progression on sorafenib. Significant improvement over placebo was also shown for the secondary endpoints of progression-free survival, time to progression, disease control, and overall tumour response."*

		Sex, n/N (%) male: I: 333/379 (88%) C: 171/194 (88%) Groups comparable at baseline? Yes.			N=21/374 (5.6%) Progressive disease, clinical progression N=56/374 (14.9%) adverse event associated with disease progression N=46/374 (12.6%) adverse event not associated with disease progression N=1/374 (0.3%) adverse event N=5/374 (1.3%) death N=25/374 (6.7%) withdrawal by patient N=2/374 (0.5%) non-compliance with study drug N=1/374 (0.3%) physician decision N=1/374 (0.3%) protocol violation	C: 8/193 (4%) P=0.0047 <u>Adverse events</u> Treatment-emergent Grade 3 I: 208/374 (56%) C: 61/193 (32%) Grade 4 I: 40/374 (11%) C: 14/193 (7%) Treatment-emergent drug-related Grade 3 I: 173/374 (46%) C: 31/193 (16%) Grade 4 I: 14/374 (4%) C: 1/193 (1%) *A detailed record of all adverse events is reported in the article.* <u>Quality of life</u> *EQ-5D index* I: 0.76 C: 0.77 Difference = -0.01 (95% CI; -0.03 to 0.02) *EQ-5D VAS* I: 71.68 C: 73.45	

					Control: 183/193 (94.8%) discontinued treatment Primary reason: N= 119/193 (61.7%) progressive disease, radiological progression N=14/193 (7.3%) Progressive disease, clinical progression N=1/193 (0.5%) Progressive disease N=28/193 (14.5%) adverse event associated with disease progression N=12/193 (6.2%) adverse event not associated with disease progression N=3/193 (1.6%) protocol violation	Difference = -1.77 (95% CI; -3.58 to 0.04) *FACT-General* I: 75.14 C: 76.55 Difference = -1.41 (95% CI; -2.93 to 0.11) *FACT-Hep* I: 129.31 C: 133.17 Difference = -3.85 (95% CI; -6.06 to -1.65)	

					N=5/193 (2.6%) withdrawal by patient N=1/193 (0.5%) other		

Risk of bias table

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**
First-line treatments							
Finn, 2020	Definitely yes; Reason: Randomization was performed through an interactive voice-response or Web-response system in stratified permuted blocks	Definitely yes; Reason: Central allocation	Probably no; Reason: Open-label trial. A blinded independent review of imaging for progression-free survival was selected for the coprimary end point.	Probably yes; Numbers and reasons for loss to follow-up are not infrequent. Reasons for missing outcome data unlikely to be related to outcome	Definitely yes; Reason: All outcome measures described in the trial protocol are reported in the results	Probably yes; Reason: No information	**LOW**
Llovet, 2008	Definitely yes; Reason: Randomization was performed by	Definitely yes;	Probably yes; Reason: Participants, care providers were blinded. Not	Probably yes; Numbers and reasons for loss to follow-up are not infrequent. Reasons	Definitely yes; Reason: All outcome measures described	Probably yes; Reason: No information	**LOW**

	computer to achieve a balance between the two groups, with stratification before randomization	Reason: Central allocation	clear whether the outcome assessors were blinded	for missing outcome data unlikely to be related to outcome	in the trial protocol are reported in the results		
Cheng, 2009	Definitely yes; Reason: Randomization was performed by an interactive voice-response system.	Definitely yes; Reason: Central allocation	Probably no; Reason: Patients were blinded. Authors stated that investigators were unblinded to treatment assignment, but it is unclear from the text who was also blinded in this double-blind study	Probably yes; Numbers and reasons for loss to follow-up are not infrequent. Reasons for missing outcome data unlikely to be related to outcome	Probably no; Reason: All outcome measures described in the trial protocol are reported in the results. Data was not shown for Quality of Life.	Probably yes; Reason: No information	**Some concerns**
Kudo, 2018	Definitely yes; Reason: Randomization was performed by an interactive voice-response system	Definitely yes; Reason: Central allocation	Probably no; Reason: Open-label trial. A blinded independent review of imaging for progression-free survival was selected	Probably yes; Numbers and reasons for loss to follow-up are not infrequent.	Definitely yes; Reason: All outcome measures described in the trial protocol are reported in the results	Probably yes; Reason: No information	**LOW**
Second-line treatment							
Bruix, 2017	Definitely yes; Reason: Randomization was centralized and performed with a computer-generated allocation list	Definitely yes; Reason: Central allocation	Definitely yes; Reason: Participants, care providers, investigators and outcome assessors were blinded	Probably yes; Numbers and reasons for loss to follow-up were slightly different between the groups. Reasons for missing outcome data unlikely to be related to outcome	Definitely yes; Reason: All outcome measures described in the trial protocol are reported in the results	Probably yes; Reason: No information	**LOW**

Zoekstrategie

Embase

No.	Query	Results
#28	#25 NOT #24 RCT	**549**
#27	#19 NOT #26 1 sleutelartikel niet gevonden agv studiedesign	**1**
#26	#20 AND #21	**4**
#25	#21 AND #23	**708**
#24	#21 AND #22 SR	**376**
#23	'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	**1890400**
#22	'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**
#21	#13 AND (1-1-2008)/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)	**5604**
#20	#13 AND #19 Alle sleutelartikelen gevonden	**5**
#19	#14 OR #15 OR #16 OR #17 OR #18	**5**
#18	ramucirumab AND vs AND placebo AND as AND 'second line' AND treatment AND in AND zhu AND 2015 AND lancet	**1**
#17	sorafenib AND in AND advanced AND llovet AND 2008 AND new AND england NOT extended:ti NOT personalized:ti	**1**
#16	efficacy AND safety AND of AND regorafenib AND versus AND placebo AND in AND patients AND with AND hepatocellular AND carcinoma AND hcc AND progressing AND on AND sorafenib NOT hcc:ti	**1**
#15	lenvatinib AND vs AND sorafenib AND in AND 'first line' AND treatment AND of AND patients AND with AND unresectable AND kudo AND lancet	**1**
#14	atezolizumab AND plus AND bevacizumab AND in AND unresectable AND new AND england	**1**
#13	#11 AND #12	**14216**

#12	'sorafenib'/exp OR 'bay 43 9006':ti,ab,kw OR 'bay 439006':ti,ab,kw OR 'bay43 9006':ti,ab,kw OR 'bay439006':ti,ab,kw OR 'nexavar':ti,ab,kw OR 'sorafenib':ti,ab,kw OR 'placebo'/exp OR placebo*:ti,ab,kw	**529899**
#11	#1 AND #10	**57709**
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	**2971284**
#9	'antineoplastic agent'/exp/mj OR 'anticancerogen':ti,ab,kw OR 'antineoplastics':ti,ab,kw OR 'cancer chemotherapeutic agent':ti,ab,kw OR 'cancer inhibitor':ti,ab,kw OR 'tumor inhibitor':ti,ab,kw OR 'tumour inhibitor':ti,ab,kw OR 'anticarcinogen':ti,ab,kw OR antineoplastic:ti,ab,kw OR ((('anti cancer' OR anticancer OR antitumo?r OR carcinostat*) NEAR/3 (agent* OR drug* OR chemotherap* OR peptide*)):ti,ab,kw) OR ctla?4:ti,ab,kw	**1251409**
#8	'programmed death 1 ligand 1'/exp OR 'programmed death 1 receptor'/exp OR 'pd l1':ti,ab,kw	**69793**
#7	'protein tyrosine kinase inhibitor'/exp AND ((tyrosin* NEAR/2 kinase NEAR/2 inhibitor*):ti,ab,kw) OR 'vegfr inhibitor*':ti,ab,kw	**52644**
#6	'monoclonal antibody'/exp/mj	**254071**
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#2	'atezolizumab'/exp OR 'atezolizumab':ti,ab,kw OR 'mpdl 3280a':ti,ab,kw OR 'mpdl3280a':ti,ab,kw OR 'rg 7446':ti,ab,kw OR 'rg7446':ti,ab,kw OR 'ro 5541267':ti,ab,kw OR 'ro5541267':ti,ab,kw OR 'tecentriq':ti,ab,kw OR 'tecntriq':ti,ab,kw	**10482**
#1	'liver cell carcinoma'/exp OR ('liver cancer'/de AND 'primary tumor'/exp) OR ((hepat* NEAR/3 carcinom*):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw OR ((primary NEAR/2 liver):ti,ab,kw)	**238171**

Ovid/Medline

Search Strategy:

#	Searches	Results
20	19 not 18 RCT	428
19	15 and 17	521
18	15 and 16 SR	175
17	(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/)	1367010
16	(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/))	558807

15	14 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	3416
14	limit 13 to yr="2008 -Current"	3737
13	11 and 12	3805
12	exp Sorafenib/ or bay 43 9006.ti,ab,kf. or bay 439006.ti,ab,kf. or bay43 9006.ti,ab,kf. or bay439006.ti,ab,kf. or nexavar.ti,ab,kf. or sorafenib.ti,ab,kf. or exp Placebo Effect/ or placebo*.ti,ab,kf.	246595
11	1 and 10	25812
10	4 or 5 or 6 or 7 or 8 or 9	1430575
9	exp Antineoplastic Agents/ or anticancerogen.ti,ab,kf. or antineoplastics.ti,ab,kf. or cancer chemotherapeutic agent.ti,ab,kf. or cancer inhibitor.ti,ab,kf. or tumor inhibitor.ti,ab,kf. or tumour inhibitor.ti,ab,kf. or anticarcinogen.ti,ab,kf. or antineoplastic.ti,ab,kf. or ((anti cancer or anticancer or antitumo?r or carcinostat*) adj3 (agent* or drug* or chemotherap* or peptide*)).ti,ab,kf. or ctla?4.ti,ab,kf.	1233681
8	Programmed Cell Death 1 Receptor/ or pdl 1.ti,ab,kf. or (programmed adj3 death adj2 receptor*).ti,ab,kf.	11428
7	(exp Protein Kinase Inhibitors/ and (tyrosin* adj2 kinase adj2 inhibitor*).ti,ab,kf.) or vegfr inhibitor*.ti,ab,kf.	18023
6	exp Antibodies, Monoclonal/	263110
5	Nivolumab/ or bms 936558.ti,ab,kf. or bms936558.ti,ab,kf. or cmab 819.ti,ab,kf. or cmab819.ti,ab,kf. or mdx 1106.ti,ab,kf. or mdx1106.ti,ab,kf. or nivolumab.ti,ab,kf. or ono 4538.ti,ab,kf. or ono4538.ti,ab,kf. or opdivo.ti,ab,kf. or keytruda.ti,ab,kf. or lambrolizumab.ti,ab,kf. or mk 3475.ti,ab,kf. or mk3475.ti,ab,kf. or pembrolizumab.ti,ab,kf. or sch 900475.ti,ab,kf. or sch900475.ti,ab,kf. or "aiv 007".ti,ab,kf. or aiv007.ti,ab,kf. or e 7080.ti,ab,kf. or e7080.ti,ab,kf. or er 203492-00.ti,ab,kf. or er203492-00.ti,ab,kf. or kisplyx.ti,ab,kf. or lenvatinib.ti,ab,kf. or lenvima.ti,ab,kf. or mk 7902.ti,ab,kf. or mk7902.ti,ab,kf. or cyramza.ti,ab,kf. or imc 1121 b.ti,ab,kf. or imc 1121b.ti,ab,kf. or imc1121 b.ti,ab,kf. or imc1121b.ti,ab,kf. or ly 3009806.ti,ab,kf. or ly3009806.ti,ab,kf. or ramucirumab.ti,ab,kf. or bay 73 4506.ti,ab,kf. or bay 734506.ti,ab,kf. or bay73 4506.ti,ab,kf. or bay734506.ti,ab,kf. or regorafenib.ti,ab,kf. or resihance.ti,ab,kf. or stivarga.ti,ab,kf.	15055
4	2 and 3	374
3	Bevacizumab/ or abevmy.ti,ab,kf. or abp 215.ti,ab,kf. or abp215.ti,ab,kf. or ainex.ti,ab,kf. or altuzan.ti,ab,kf. or alymsys.ti,ab,kf. or ankeda.ti,ab,kf. or ask b1202.ti,ab,kf. or askb1202.ti,ab,kf. or avastin.ti,ab,kf. or aybintio.ti,ab,kf. or bat 1706.ti,ab,kf. or bat1706.ti,ab,kf. or "bcd 021".ti,ab,kf. or bcd021.ti,ab,kf. or bevacizumab.ti,ab,kf. or bevax.ti,ab,kf. or bevz 92.ti,ab,kf. or bevz92.ti,ab,kf. or bi 695502.ti,ab,kf. or bi695502.ti,ab,kf. or boyounuo.ti,ab,kf. or bryxta.ti,ab,kf. or byvasda.ti,ab,kf. or cbt 124.ti,ab,kf. or cbt124.ti,ab,kf.	21219

	or chs 5217.ti,ab,kf. or chs5217.ti,ab,kf. or cizumab.ti,ab,kf. or ct p16.ti,ab,kf. or ctp16.ti,ab,kf. or equidacent.ti,ab,kf. or fkb 238.ti,ab,kf. or fkb238.ti,ab,kf. or gb 222.ti,ab,kf. or gb222.ti,ab,kf. or hd 204.ti,ab,kf. or hd204.ti,ab,kf. or "hlx 04".ti,ab,kf. or hlx04.ti,ab,kf. or ibi 305.ti,ab,kf. or ibi305.ti,ab,kf. or "jy 028".ti,ab,kf. or jy028.ti,ab,kf. or krabeva.ti,ab,kf. or kyomarc.ti,ab,kf. or lextemy.ti,ab,kf. or "ly 01008".ti,ab,kf. or ly01008.ti,ab,kf. or "mb 02".ti,ab,kf. or mb02.ti,ab,kf. or mil 60.ti,ab,kf. or mil60.ti,ab,kf. or mvasi.ti,ab,kf. or myl 14020.ti,ab,kf. or myl 1402o.ti,ab,kf. or myl14020.ti,ab,kf. or myl1402o.ti,ab,kf. or nsc 704865.ti,ab,kf. or nsc704865.ti,ab,kf. or onbevzi.ti,ab,kf. or ons 1045.ti,ab,kf. or ons 5010.ti,ab,kf. or ons1045.ti,ab,kf. or ons5010.ti,ab,kf. or oyavas.ti,ab,kf. or "pf 06439535".ti,ab,kf. or pf 6439535.ti,ab,kf. or pf06439535.ti,ab,kf. or pf6439535.ti,ab,kf. or pusintin.ti,ab,kf. or ql 1101.ti,ab,kf. or ql1101.ti,ab,kf. or r 435.ti,ab,kf. or r435.ti,ab,kf. or rg 435.ti,ab,kf. or rg435.ti,ab,kf. or rhumab-vegf.ti,ab,kf. or ro 4876646.ti,ab,kf. or ro4876646.ti,ab,kf. or "rph 001".ti,ab,kf. or rph001.ti,ab,kf. or sb 8.ti,ab,kf. or sb8.ti,ab,kf. or sct 510.ti,ab,kf. or sct510.ti,ab,kf. or stc 103.ti,ab,kf. or stc103.ti,ab,kf. or "tab 008".ti,ab,kf. or tab008.ti,ab,kf. or tot 102.ti,ab,kf. or tot102.ti,ab,kf. or "trs 003".ti,ab,kf. or trs003.ti,ab,kf. or tx 16.ti,ab,kf. or tx16.ti,ab,kf. or versavo.ti,ab,kf. or zirabev.ti,ab,kf. or zrc 113.ti,ab,kf. or zrc113.ti,ab,kf.	
2	(atezolizumab or mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or ro 5541267 or ro5541267 or tecentriq or tecntriq).ti,ab,kf.	1957
1	Carcinoma, Hepatocellular/ or (hepat* adj3 carcinom*).ti,ab,kf. or hepatocarcinom*.ti,ab,kf. or hepatoma.ti,ab,kf. or (liver adj3 primary).ti,ab,kf.	162623

Module 7-1 Hepatocellulair carcinoom – Radioembolisatie

Uitgangsvraag

Wat is de plaats van radioembolisatie bij hepatocellulair carcinoom met BCLC stage 0-B in vergelijking met TACE?

Inleiding

In het huidige Barcelona Clinic Liver Cancer (BCLC) behandelschema wordt radioembolisatie als behandeloptie voorgesteld in (very) early stage (stage 0-A). Dit is in 2022 toegevoegd. In Nederland wordt in de praktijk radioembolisatie doorgaans toegepast in BCLC stage A-C. In deze module wordt gekeken naar de rol van radioembolisatie in BCLC stage 0-B in vergelijking met TACE.

Search and select

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

What is the effectiveness of transarterial radioembolization (TARE) versus transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma with BCLC stage 0-B?

P: patients with hepatocellular carcinoma with BCLC stage 0-B;
I: radioembolization (transarterial radioembolization (TARE));
C: chemoembolization (transarterial chemoembolization (TACE));
O: local tumor control, response rate, success rate, overall survival, progression-free survival, complications.

<u>Relevant outcome measures</u>

The guideline development group considered local tumor control, response rate and success rate as critical outcome measures for decision making; and overall survival, progression-free survival, quality of life and complications as important outcome measures for decision making.

The guideline development group defined the outcome measures as follows:

- Local tumor control: Lack of tumor progression (complete response + partial response + stable disease).
- Response rate: Complete response (disappearance of all target lesions) + partial response (at least 30% decrease in the sum of target lesions).
- Success rate: Rate of downstaging success (decrease of tumor burden to within Milan criteria) + rate of bridging success (patients receiving a liver transplantation after neo-adjuvant therapy).
- Overall survival: Time to death from any cause with a minimum follow-up of one year.
- Progression-free survival: Time from randomization or initiation of treatment to the occurrence of disease progression or death from any cause.
- Complications: Adverse events following treatment (grade 3 and higher or major/serious adverse events).

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

- Local tumor control: Absolute difference >5%.
- Response rate: Absolute difference >5%.
- Success rate: Absolute difference >5%.

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

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 01-01-2000 until 08-02-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 340 hits.

Studies were selected based on the following criteria:

- Systematic reviews or randomized controlled trials;
- full-text English language publication;
- complying with the PICO criteria.

Forty-three studies were initially selected based on title and abstract screening. After reading the full text, 42 studies were excluded (see the table with reasons for exclusion under the tab Methods). One systematic review comparing radioembolization to chemoembolization was selected. One additional RCT was included.

Results

One systematic review was selected, of which three RCTs were extracted. One additional RCT was included, resulting in four studies for 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

Yang (2020) conducted a systematic review on transarterial strategies for the treatment of unresectable hepatocellular carcinoma. The effects of TARE, conventional TACE and drug-eluting beads (DEB-TACE) on overall survival, tumor response, and complications were evaluated. Multiple databases (PubMed, EMBASE, Google Scholar, and Cochrane) were searched up to July 2019. Twenty-eight studies were included, of which eight randomized controlled trials (RCTs). In three RCTs **(Kolligs, 2015; Pitton, 2015; Salem, 2016)**, TACE was compared with TARE. The other five RCTs were not evaluated in this literature analysis, as these compared conventional TACE to DEB-TACE.

Kolligs (2015) investigated the quality of life, efficacy and safety of TARE compared to conventional TACE in an open-label multicenter pilot study (the *SIRTACE* study). Patients with unresectable HCC, Child-Pugh ≤B7, ECOG performance status ≤2 and ≤5 liver lesions (≤20 cm total maximum diameter) without extrahepatic spread were considered eligible. Patients with BCLC stage C were also included. Any patients with significant extrahepatic uptake on ^{99m}Tc-MAA scan precluding safe administration of TARE or >15% arteriovenous shunting from liver to lungs were excluded. A total of 13 patients was randomized into the TARE group (mean age 65.8±6.7; 85% male) and 15 into the cTACE group (mean age 66.7±9.0; 87% male). Only 18 of 28 complete cases were available for statistical analysis.

Pitton (2015) investigated the efficacy of TARE compared to DEB-TACE in a prospective, single-center, randomized trial. Patients with histologically proven unresectable N0, M0 HCC

were included. The main exclusion criteria were feasibility for curative treatment, previous TACE or TARE, Child-Pugh stage C, BCLC stage C, ECOG performance status >0, tumor involvement >50% of the liver and extrahepatic tumor spread. A total of 12 patients was randomized into the TARE group (mean age 71.8±7.2; 67% male) and 12 into the DEB-TACE group (mean age 70.5±9.0; 83% male).

Salem (2016) compared the effects of TARE and conventional TACE in a randomized, phase 2 study (the *PREMIERE* study). Inclusion criteria were image/biopsy-proven HCC by guidelines, unablatable/unresectable disease, no vascular invasion, Child–Pugh A/B, bilirubin level of 2.0 mg/dL or less, and aspartate aminotransferase/alanine aminotransferase 5 times the upper limit of normal or less. Exclusion criteria were infiltrative/bulky disease (≥70% tumor burden), 50% or more tumor burden with albumin level less than 3 g/dL, cardiac comorbidities, major surgery within the past 4 weeks, or active infection. A total of 24 patients was randomized into the TARE group (median age 62, 95% CI 58 to 65; 71% male) and 21 into the cTACE group (median age 64, 95% CI 62 to 70; 76% male). The study was halted early because of slow accrual and competing studies.

One additional RCT was published after the search date of the systematic review by Yang (2020).

Dhondt (2022) investigated the efficacy and safety of TARE compared to DEB-TACE in a single-center prospective randomized controlled trial (the *TRACE* study). Patients with intermediate-stage HCC, extended to ECOG performance status 1 and those with early-stage HCC not eligible for surgery or thermoablation were considered eligible. Exclusion criteria were greater than 50% liver involvement, extrahepatic disease, invasion of the main, right, or left portal vein, bilirubin over 34 mmol/L, or over 44 mmol/L in case of a single involved segment, and Child-Pugh score higher than 7. A total of 38 patients was randomized into the TARE group (median age 67, IQR 63-72; 87% male) and 34 into the DEB-TACE group (median age 68, IQR 61-71; 88% male). The study was terminated early: the statistical conditions at interim analysis were fulfilled to reject the null hypothesis and request a halt of the study.

Results

Local tumor control (critical)

Two studies reported local tumor control.

Kolligs (2015) reported a local tumor control of 76.9% (10/13 patients) for the TARE group and 73.3% (11/15 patients) for the cTACE group and. The risk difference is 3.6%, which is not clinically relevant.

Salem (2016) defined local tumor control by enhancement criteria (WHO/EASL) and new lesions. TARE showed better local tumor control than cTACE (table 1, pattern of progression).

Table 7.1 Pattern of Progression (Salem, 2016)

Characteristic	TARE (n=23)	cTACE (n=19)
WHO	1 (4%)	5 (26%)
EASL	0 (0%)	8 (42%)
New hepatic lesions	1 (4%)	6 (32%)
Extrahepatic metastases	0 (0%)	2 (11%)

Response rate *(critical)*
Three studies reported response rate.

Kolligs (2015) reported a partial response rate (RECIST 1.0) of 30.8% (4/13 patients) for the TARE group and 13.3% (2/15 patients) for the cTACE group. The risk difference is 17.4%, which is clinically relevant.

Salem (2016) based the rate of response on tumor size and necrosis criteria. The EASL response was 87% (20/23 patients) for the TARE group and 74% (14/19 patients) for the cTACE group. The risk difference is 13.3%, which is clinically relevant.

Dhondt (2022) described the response rate as the percentage of participants whose best response was complete or partial according to the modified RECIST criteria. The response rate in the treated area was 94% for the TARE group and 100% for the DEB-TACE group. The response rate in the liver was 88% for the TARE group versus 87% for the DEB-TACE group. The risk differences are 6.0% and 1.0% for the treated area and the liver respectively. The risk difference for response rate in the treated area is clinically relevant. The risk difference for response rate in the liver is not clinically relevant.

Success rate *(critical)*
All studies reported the success rates of downstaging and/or bridging to transplant.

Kolligs (2015) reported one patient who was downstaged to liver transplantation in the TARE group (1/13 patients, 7.7%), and two patients in the cTACE group (2/15 patients, 13.3%). The risk difference is 5.6%, which is clinically relevant.

Pitton (2014) reported one patient who underwent liver transplantation in the DEB-TACE group.

Salem (2016) reported the rates of transplantation in listed patients. In the TARE group, 13 patients underwent transplantation (13/15 listed patients, 86.7%) at a median of 8.8 months (range, 4.0 to 15.3 months). In the cTACE group, 7 patients underwent transplantation (7/10 listed patients, 70.0%) at a median of 7.6 months (range, 3.0 to 17.3 months). The risk difference is 16.7%, which is clinically relevant.

Dhondt (2022) reported 10 participants in whom downstaging led to transplant in the TARE group (10/38 patients, 26.3%) and 4 patients in the DEB-TACE group (4/34 patients, 11.8%). The risk difference is 14.5%, which is clinically relevant.

Overall survival *(important)*
Four studies reported overall survival.

Kolligs (2015) reported a 1-year OS rate of 46.2% (6/13 patients) for the TARE group and 66.7% (10/15) for the cTACE group. The risk difference is 20.5%, which is clinically relevant.

Pitton (2015) reported a median OS of 19.4 months for the TARE group and 25.9 months for the DEB-TACE group. The hazard ratio was not reported. The difference in median OS (6.5 months in favor of the DEB-TACE group) was considered as clinically relevant.

Salem (2016) reported a median OS of 18.6 months (95% CI 7.4 to 32.5) for the TARE group and 17.7 (95% CI 8.3 to not calculable) months for the cTACE group. The hazard ratio was

not reported. The difference in median OS (0.9 months in favor of the TARE group) was considered as not clinically relevant.

Dhondt (2022) reported a median OS of 30.2 months after TARE and 15.6 months after DEB-TACE (HR 0.48; 95% CI 0.28 to 0.82). The difference in median OS (14.6 months in favor of the TARE group) was considered as clinically relevant.

Progression-free survival *(important)*
Three studies reported progression-free survival (PFS).

Kolligs (2015) reported a median PFS of 3.6 months (95% CI 2.3 to 6.2) for the TARE group and 3.7 months (95% CI 1.6 to 11.0) for the cTACE group. The hazard ratio was not reported. The difference in median PFS (0.1 months in favor of the cTACE group) was considered as not clinically relevant.

Pitton (2015) reported a median PFS of 5.9 months for the TARE group and 7.1 months for the DEB-TACE group. During follow-up, seven patients died in each group (7/12 patients, 58.3% for both groups). The hazard ratio was not reported. The difference in median PFS (1.2 months in favor of the DEB-TACE group) was considered as clinically relevant.

Dhondt (2022) reported a median PFS of 11.8 months after TARE and 9.1 months after DEB-TACE (HR 0.40; 95% CI 0.24 to 0.67). The difference in median PFS (2.7 months in favor of the TARE group) was considered as clinically relevant.

One study reported time to progression (TTP).

Salem (2016) reported that the TTP was not reached for the TARE group (>26 months). The median TTP for the cTACE group was 6.8 months (HR 0.122; 95% CI 0.027 to 0.557). This difference was considered as clinically relevant.

Complications *(important)*
Two studies reported complications.

Kolligs (2015) reported two serious treatment-related adverse events in the TARE group (2/13 patients) and two in the cTACE group (2/15 patients). These included grade 3 infection (TARE and cTACE), grade 3 post-TACE syndrome accompanied by a grade 4 increase in AST (cTACE), and grade 3 hyperbilirubinemia (TARE).

Salem (2015) reported grade 3 or 4 clinical toxicities and laboratory toxicities. In the TARE group, there was one clinical toxicity (abdominal pain, 1/24 patients). In the cTACE group, there were no clinical toxicities (0/19 patients). There were five laboratory toxicities in the TARE group (↑ serum bilirubin (1/19), ↑ AST (2/19), neutropenia (2/19)) and four in the cTACE group (↓ albumin (1/24), ↑ serum bilirubin (2/24), leukopenia (1/24)).

Pitton (2015) listed causes of death and clinical events in both groups but did not report numbers of serious adverse events for both groups.

Level of evidence of the literature

The level of evidence of randomized controlled trials is considered high according to the GRADE methodology. Therefore, the level of evidence of these cohort studies starts at high GRADE.

Local tumor control

The level of evidence regarding the outcome measure **local tumor control** was downgraded by two levels because of study limitations (risk of bias (see RoB assessment), -1) and low number of patients (imprecision, -1). The level of evidence was therefore graded as low.

Response rate

The level of evidence regarding the outcome measure **response rate** was downgraded by three levels because of study limitations (risk of bias (see RoB assessment), -1), indirectness (-1; use of different treatment regimens in the control group) and low number of patients (imprecision, -1). The level of evidence was therefore graded as very low.

Success rate

The level of evidence regarding the outcome measure **success rate** was downgraded by three levels because of study limitations (risk of bias (see RoB assessment), -1), indirectness (-1; use of different treatment regimens in the control group) and low number of patients (imprecision, -1). The level of evidence was therefore graded as very low.

Overall survival

The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (risk of bias (see RoB assessment), -1), indirectness (-1; use of different treatment regimens in the control group) and low number of patients (imprecision, -1). The level of evidence was therefore graded as very low.

Progression-free survival

The level of evidence regarding the outcome measure **progression-free survival** was downgraded by three levels because of study limitations (risk of bias (see RoB assessment), -1), indirectness (-1; use of different treatment regimens in the control group) and low number of patients (imprecision, -1). 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 (risk of bias (see RoB assessment), -1), indirectness (-1; use of different treatment regimens in the control group) and low number of patients (imprecision, -1). The level of evidence was therefore graded as very low.

Conclusions

Local tumor control

Low GRADE	Radioembolization (TARE) may result in a higher **local tumor control** than chemoembolization (TACE) in patients with hepatocellular carcinoma with BCLC stage 0-B, but the evidence is uncertain. *Sources: (Kolligs, 2015; Salem, 2016)*

Response rate

Very low GRADE	Radioembolization (TARE) may result in a higher **response rate** than chemoembolization (TACE) in patients with hepatocellular carcinoma with BCLC stage 0-B, but the evidence is very uncertain. *Sources: (Kolligs, 2015; Salem, 2016; Dhondt, 2022)*

Success rate

Very low GRADE	Radioembolization (TARE) may result in a higher **success rate** than chemoembolization (TACE) in patients with hepatocellular carcinoma with BCLC stage 0-B, but the evidence is very uncertain. *Sources: (Kolligs, 2015; Pitton, 2015; Salem, 2016; Dhondt, 2022)*

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of radioembolization (TARE) on **overall survival** compared with the effect of chemoembolization (TACE) in patients with hepatocellular carcinoma with BCLC stage 0-B. *Sources: (Kolligs, 2015; Pitton, 2015; Salem, 2016; Dhondt, 2022)*

Progression-free survival

Very low GRADE	The evidence is very uncertain about the effect of radioembolization (TARE) on **progression-free survival** compared with the effect of chemoembolization (TACE) in patients with hepatocellular carcinoma with BCLC stage 0-B. *Sources: (Kolligs, 2015; Pitton, 2015; Salem, 2016; Dhondt, 2022)*

Complications

Very low GRADE	The evidence is very uncertain about the effect of radioembolization (TARE) on **complications** compared with the effect of chemoembolization (TACE) in patients with hepatocellular carcinoma with BCLC stage 0-B. *Sources: (Kolligs, 2015; Pitton, 2015; Salem, 2016)*

Overwegingen – van bewijs naar aanbeveling

Kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met transarteriële radio-embolisatie (TARE) in vergelijking met transarteriële chemo-embolisatie (TACE) bij patiënten met hepatocellulair carcinoom met BCLC stage 0-B. Er werden vier gerandomiseerde gecontroleerde studies (RCTs) geselecteerd en uitgewerkt (Dhondt, 2022; Kolligs, 2015; Pitton, 2015; Salem, 2016).

Er werden alleen RCTs geïncludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. De geïncludeerde studies hadden in wisselende mate methodologische beperkingen (risk of bias). Er was in sommige studies een risico op bias door onder andere ontoereikende documentatie, loss to follow-up en blindering. Daarnaast waren de studiebevindingen soms moeilijk met elkaar te vergelijken omdat de controle interventies van elkaar verschilden (indirectheid) en waren er meerdere studies met een relatief kleine populatie en mede hierdoor een grote spreiding van de puntschatter van de uitkomstmaat (imprecisie), waardoor de kwaliteit van dit bewijs ook naar beneden werd bijgesteld. De

bewijskracht van de literatuur werd voor zowel de cruciale als belangrijke uitkomstmaten, door bovenstaande bevindingen gegradeerd als ‘laag’ of ‘zeer laag’.

Klinische studies naar het gebruik van medische hulpmiddelen kennen beperkingen in vergelijking met geneesmiddelenstudies. In het geval van TARE, waarbij radioactieve medische hulpmiddelen gebruikt worden, betreft het een complexe techniek en logistiek. Vanwege relatief beperkte financiële middelen is daarnaast het vinden van een haalbaar en tegelijk betekenisvol eindpunt een uitdaging. In Nederland en andere landen behoort TARE momenteel tot de vergoede zorg voor HCC. Daarmee is TARE routinezorg, wat het uitvoeren van (vergelijkende) studies verder bemoeilijkt. Patiënten en behandelaars hebben namelijk vaak een voorkeur voor de studie arm (TARE) in vergelijking met de controle arm (TACE). De moeizame en langdurige inclusie van de PREMIERE studie (Salem, 2016) is daar een voorbeeld van. De resulterende studies hebben daardoor vaak een beperkte studiepopulatie, ondanks langdurige inclusie, en werden om die reden vaak voortijdig beëindigd. Bovendien is de beschikbare data beperkt en gaat niet verder dan progressievrije overleving. Voor TARE in deze setting is de beschikbare data echter toch van waarde.

De data van de beschreven vergelijkende studies werden bevestigd in verschillende cohortstudies. In ‘early stage’ BCLC 0 ziekte werd een objectieve respons gerapporteerd bij 88 tot 100% van de patiënten met een mediane solitaire tumor grootte van 2.1 tot -2.7 cm, met een maximum van 8 cm (target laesie progressie was 0-4% na 1 jaar en 0-12% na 2 jaar). Dit leidde tot inclusie van TARE in het BCLC schema als een alternatieve behandeling van HCC patiënten bij wie conventionele ablatieve technieken niet mogelijk zijn of hebben gefaald (Salem, 2021; Kim, 2022). In de grootste cohortstudie in 209 patiënten (BCLC A, n=27; BCLC B, n=68; BCLC C, n=114) werd een respons gevonden in 62% van de patiënten, met een mediane overleving van 20,3 maanden (95%CI = 16.7 tot 26.4 maanden)(Lam, 2022).

In de gepresenteerde studies werden verschillende producten gebruikt in beide armen, i.e. conventionele TACE of DEB-TACE versus hars of glas yttrium-90 (^{90}Y)-TARE. Elk product werd in twee van de vier studies toegepast en dus kruislings vergeleken. Belangrijk daarbij is dat conventionele TACE equivalent is aan DEB-TACE in deze setting (Lammer, 2010; Bzeizi, 2021). Dit mag ook verwacht worden van hars versus glas ^{90}Y-TARE, er zijn echter nooit ‘head-to-head’ studies uitgevoerd. In de dagelijkse routine zullen de beschikbare producten door elkaar gebruikt worden, waarbij ook holmium-166 (^{166}Ho)-TARE (Reinders, 2022) vergelijkbare resultaten laat zien. Het Zorginstituut Nederland beschouwt de drie verschillende producten dan ook als ‘technisch equivalente varianten’ van TARE.

Concluderend laten de vier geïncludeerde studies aanwijzingen zien voor een mogelijk positief effect van TARE op lokale tumorcontrole, respons en succespercentage (downstaging/bridging) in vergelijking met TACE. Er werden klinisch relevante verschillen gevonden voor meerdere uitkomstmaten, maar de algehele bewijskracht is onvoldoende om hier een eenduidige conclusie uit te trekken.

<u>Voor- en nadelen van de interventie (TARE)</u>
TACE is in de analyse beschouwd als de controle arm, omdat dit momenteel de (inter)nationale standard of care is bij irresectabele BCLC 0-B patienten bij wie ablatieve technieken niet mogelijk zijn.

Patiënten met een tumor trombus in de vena porta (PVT) worden, in tegenstelling tot TACE, wel behandeld middels TARE. Bovendien kunnen patiënten met beperkte ziekte buiten de

lever, meerdere tumoren (>3-5) en grotere tumoren (>5 cm) baat hebben van TARE als een lokale behandeloptie in plaats van systemische behandeling. TARE heeft dus een bredere indicatie dan TACE. De DOSISPHERE-01 studie includeerde 41/60 patiënten met PVT en een protocollaire tumor grootte van >7 cm met een geïncludeerde gemiddelde grootte van >10 cm. Maar ook in eerdere stadia (zonder PVT) werden grotere tumoren middels TARE behandeld met een solitaire tumor grootte van maximaal 8 cm (Salem, 2021). De belangrijkste uitgevoerde studies naar TACE versus 'best supportive care' includeerden tumoren met een kleinere gemiddelde grootte van 4,9 cm (Llovet, 2002) en 7,0 cm (Lo, 2002) met gemiddeld 2,8 TACE behandelingen (range 1-8) en 4,5 TACE behandelingen (range 1 tot 15), respectievelijk.

De beschreven studies in deze analyse gebruikten allen een zogenaamde niet-geïndividualiseerde methode. Dit betekende dat voor alle behandelingen een gemiddelde dosis gehanteerd werd in plaats van een geïndividualiseerde dosis, waarbij voor iedere individuele patiënt een voldoende effectieve tumor dosis berekend wordt met een acceptabel veilige dosis in het omringende leverweefsel. Verschillende studies leverden bewijs voor deze benadering in HCC (Garin, 2021). In de DOSISPHERE-01 studie werden 60 'intermediate/advanced stage' BCLC B-C HCC patiënten gerandomiseerd voor beide benaderingen. De gevonden respons verdubbelde in de studie arm (36% versus 71%; $p < 0.0001$), wat leidde tot verbetering van de algehele en progressievrije overleving. Het is waarschijnlijk dat bij gebruik van een individueel behandelplan voor TARE, de resultaten in vergelijking met TACE verder zullen verbeteren. In Nederland wordt deze geïndividualiseerde benadering overal toegepast en beschouwd als 'state-of-the-art' TARE, waarbij gepubliceerde internationale richtlijnen geconsulteerd kunnen worden (Weber, 2022).

Een nadeel van TARE is de complexiteit van het gehele behandeltraject. Dit geldt voor selectie van de juiste patienten, de voorbereidende angiografie, behandelstrategie, het opstellen van een persoonlijk behandelplan, de complexe keten van bestellen, plannen, productie en levering van de radioactieve microsferen, en de bijbehorende stralingshygienische maatregelen.

<u>Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)</u>
TACE bestaat meestal uit meerdere behandelingen, meer dan TARE, en kan daarmee als meer belastend worden ervaren. Zowel TACE als TARE worden goed verdragen, er is geen bewijs dat TACE of TARE meer of minder complicaties zou laten zien.

<u>Kosten (middelenbeslag)</u>
Er werden verschillende studies uitgevoerd naar de kosteneffectiviteit van TARE in vergelijking met TACE. In een studie uit de Verenigde Staten bij >5000 HCC patiënten uit de 'United Network for Organ Sharing' (UNOS) database (solitair HCC <3 cm; overbrugging naar transplantatie) had thermale ablatie de beste kosteneffectiviteit, gevolgd door TARE en TACE. Ten opzichte van TACE had TARE een betere kosteneffectiviteit met een 'incremental cost-effectiveness ratio' van 29.600 dollar/QALY (Wu, 2023).

De betere kosteneffectiviteit van TARE wordt voornamelijk verklaard door het feit dat TACE uit meerdere behandelingen bestaat. Dit werd bevestigd in een studie waarbij dit de enige variabele was die de optimale strategie deed veranderen van TACE naar TARE (Ray, 2012).

De betere kosteneffectiviteit van TARE werd daarnaast ook bevestigd in patiënten met meer uitgebreide ziekte, grotere tumoren en meer tumoren. Hierbij speelt ook weer het aantal

TACE behandelingen dat nodig is om de meer uitgebreide ziekte adequaat te behandelen eenn grote rol bij de betere kosteneffectiviteit van TARE in vergelijking met TACE (Rostambeigi, 2014).

Aanvaardbaarheid, haalbaarheid en implementatie
De werkgroep is van mening dat er geen bezwaren of voorwaarden zijn voor aanvaardbaarheid, haalbaarheid of implementatie van de aanbeveling.

Aanbeveling

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Een aantal criteria leidt tot falen van TACE in 'intermediate stage' BCLC B HCC. Deze criteria zijn tumor grootte (>5 cm) en aantal (>3 tumoren). Dit werd bevestigd met klinische data (Kudo, 2014; Yamakado, 2014). Mede om die reden raden experts aan om TACE superselectief toe te passen, in patiënten met <5 tumoren, met een maximum van twee aangedane segmenten, en alleen bij tumoren <5 cm (de Baere, 2022).

Aanwezigheid van PVT, het aantal benodigde behandelcycli (kosteneffectiviteit), tumor grootte en tumor aantal, zijn belangrijke criteria die de individuele keuze voor TARE kunnen bepalen, zeker als het opstellen van een persoonlijk behandelplan daarin meegenomen wordt.

Beslis multidisciplinair in een centrum met expertise op het gebied van behandeling van HCC (referentie naar nieuwe SONCOS richtlijnen van 2023) of voor patiënten met een HCC met BCLC stage 0-B, bij wie geen resectie of ablatie mogelijk is, TARE danwel TACE de voorkeur heeft.

Overweeg of TARE de voorkeur heeft op basis van:
- Aanwezigheid van vena porta tumor trombus (PVT)
- Falen van TACE (of niet mogelijk)
- Grootte (circa >5 cm)
- Aantal tumoren (>3-5)
- Aangedane leversegmenten (>2)

Selectie van patienten voor TARE en het uitvoeren van TARE zelf dient te gebeuren op basis van dosimetrie, i.e. een voldoende effectieve tumor dosis en veilige dosis op het omringende leverweefsel.

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Bijlagen bij module 7.1

Kennislacunes

De combinatie van TARE en systeemtherapie (e.g. immuuntherapie) in BCLC stage 0-B is (nog) niet onderzocht. De combinatie en het vergelijken van TARE en sorafenib is wel onderzocht in BCLC stage C (zie module X), maar hierbij werd niet gebruik gemaakt van state-of-the-art TARE. Het ligt in de lijn der verwachting dat combinaties van lokale behandelopties en systeemtherapie in de toekomst een grotere rol gaan spelen.

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
1e							
2e							
etc							

[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, et cetera.

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

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

Evidence tables

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

Research question: What is the effectiveness of radioembolization versus transarterial chemoembolization in patients with hepatocellular carcinoma with BCLC stage 0-B?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Kolligs, 2015 *SIRTACE study*	Type of study: RCT Setting and country: University of Munich, Germany, and the Clinica Universidad de Navarra, Pamplona, Spain. Funding and conflicts of interest: the work was supported by SIRTEX Medical Europe GmbH. Multiple authors received either a research grant and/or honoraria from Sirtex Medical Ltd.	<u>Inclusion criteria</u>: - adults (≥18 years) with confirmed unresectable HCC - preserved liver function (Child-Pugh ≤B7; total bilirubin ≤2 mg/dl) - ECOG performance status ≤2 - absence of vascular invasion or extrahepatic spread - ≤5 liver lesions (≤20 cm total maximum diameter) including at least one quantifiable lesion, or a single lesion ≤10 cm <u>Exclusion criteria</u>: - significant extrahepatic uptake on 99mTc-MAA scan precluding safe administration of SIRT - >15% arteriovenous shunting from liver to lungs	Selective internal radiation therapy within 14 days of the initial hepatic arteriogram: selective intraarterial implantation of 0.5–3 GBq ^{90}Y-resin microspheres as a lobar, segmental treatments or whole-liver approach during a single session.	Transarterial chemoembolization (epirubicin 50 mg/m^2, lipiodol and embolizing agent). Repeat TACE was conducted every 6 weeks until tumour enhancement was not observed on MRI or until tumour progression was confirmed according to current expert guidance.	Follow-up: 6-weekly from the day of first treatment procedure for at least 12 months or until death or last follow-up on 11 October 2012. Length of follow-up: median 10.7 months (95% CI 7.6–25.5), not specified per group. Loss-to-follow-up: Intervention: 10 (76.9%) Control: 9 (60.0%)	Local tumor control: I: 76.9% C: 73.3% Partial response rate (RECIST): I: 30.8% C: 13.3% Downstaging leading to transplantation: I: 1/13, 7.7% C: 2/15, 13.3% Survival 6 months: I: n=9/13, 69.2% C: n=13/15, 86.7% Survival 12 months: I: n=6/13, 46.2% C: n=10/15, 66.7%	Conclusion authors: Both procedures appeared to be well tolerated without any deleterious effects on HRQoL. However, patients receiving TACE required a significantly greater number of procedures, while repeat SIRT is rarely deemed necessary or recommended for patients with HCC. Like TACE, SIRT was effective for the local control of liver disease and may also have a role in rendering unresectable patients eligible for transplantation.

		N total at baseline: Intervention: 13 Control: 15 Important prognostic factors[2]: *age ± SD:* *I: 65.8 ± 6.7* *C: 66.7 ± 9.0* *Sex:* *I: 85% M* *C: 87% M* *BCLC stage:* *I: 38.5% A, 38.5% B, 23% C* *C: 27% A, 53% B,* *20% C* Groups comparable at baseline? Yes			*(death during study follow-up)* Incomplete outcome data: Not reported.	PFS (median, 95% CI): I: 3.6 (2.3-6.2) months C: 3.7 (1.6-11.0) months Treatment related AE (serious): I: 2/13, 15.4% C: 2/15, 13.3%	
Pitton 2015	Type of study: RCT Setting and country: Johannes Gutenberg University Medical Center, Germany Funding and conflicts of interest: the authors have nothing to disclose.	Inclusion criteria: - *≥18 years* - *confirmed HCC* - *intermediate stage HCC (BCLC stage B)* - *≥1 measurable lesion in MRI* - *tumor load ≤50%* - *preserved liver function (Child Pugh A – B7)* Exclusion criteria: - *patients feasible for curative treatment*	SIRT was performed using resin-based 90Y loaded microparticles. The activity and dose for 90Y-SirSpheres were calculated according to the body surface model. SIRT was performed in a lobar approach. In	TACE was performed using drug-eluting beads loaded with a maximum dose of 150 mg Doxorubicin per session. The beads were administrated super selectively at the level of segmental and subsegmental arteries until stasis was reached (embolization endpoint). In patients with multilocular tumor spread or bilobar disease preventing a selective approach, a	Follow-up: every 3 months until clinical endpoints were reached. Length of follow-up: days *± SD:* *I: 435 ± 320* *C: 404 ± 304*	Liver transplantation I: 1 patient C: 0 patients OS: I: 592 days C: 788 days PFS: I: 180 days C: 216 days	Conclusion authors: This randomized pilot study suggests SIRT and TACE are equivalent in terms of progressionfree survival, overall survival, and TTP in intermediate stage HCC patients. The lower rate of tumor progression in the SIRT group was

		- previous TACE or SIRT *- chemotherapy during the last 4 weeks* *- Child Pugh stage C* *- BCLC stage C* *- ECOG Performance Status >0* *- tumor involvement >50 % of the liver* *- extrahepatic tumor* *- serum bilirubin >2.0 mg/dl; serum albumin 2.8 g/dl, serum creatinine >2 mg/dl; leukocytes <3,000/ml; thrombocytes <50,000/ml* *- clinically apparent ascites* *- esophageal bleeding during the last 3 months* *- hepatic encephalopathy* *- transjugular intrahepatic portosystemic shunt (TIPS)* *- infiltration or occlusion of the portal vein* *- hepatopulmonary shunt ≥20% in the MAA scan* *- contraindications against angiography* *- gravidity* <u>N total at baseline</u>: Intervention: 12 Control: 12 <u>Important prognostic factors</u>[2]:	case of bilobar tumor spread, treatment was split in two sessions. In these cases, the first treatment was dedicated to the liver lobe with the greater tumor volume. Treatment of the contra-lateral lobe was scheduled after 4 weeks to preserve liver function.	less selective embolization technique was used and each session was limited to one liver lobe according to the discretion of the investigator. In those cases, the contralateral lobe was treated after 4 weeks. TACE was repeated every 6 weeks until no more viable tumor was detected by MRI.	Loss-to-follow-up: Intervention: 0 (0.0%) Control: 0 (0.0%) Incomplete outcome data: Intervention: 0 (0.0%) Control: 0 (0.0%) Patients with crossover from SIRT to TACE were not censored.		nullified by a greater incidence of liver failure.

		age ± SD: *I: 71.8 ± 7.2* *C: 70.5 ± 9.0* *Sex:* *I: 67% M* *C: 83% M* *BCLC stage:* *I: 100% B* *C: 100% B* Groups comparable at baseline? Yes					
Salem, 2016 *PREMIERE study*	Type of study: RCT Setting and country: Northwestern University/Memorial Hospital, Chicago Funding and conflicts of interest: this study was supported in part by National Institutes of Health grant CA126809. Also supported by a Medical Scientist Training Program student (T32GM008152 to A.C.G.) with support for research provided by an Allied Scientist	Inclusion criteria: - image/biopsy-proven HCC by guidelines - unablatable/ unresectable disease - no vascular invasion - Child–Pugh A/B - bilirubin level of 2.0 mg/dL or less - aspartate aminotransferase/alanine aminotransferase 5 times the upper limit of normal or less Exclusion criteria: - infiltrative/bulk disease (70% tumor burden) - 50% or more tumor burden with albumin level less than 3 g/dL	Angiography and technetium-99m scintigraphy were used to estimate lung shunting, identify extrahepatic perfusion, and perform coil embolization if necessary. Glass microspheres were used at a 120-Gy dose, with treatment on an outpatient basis.	Chemoembolization was performed with 75 mg/m^2 (maximum, 150 mg) dosing. The drug/lipiodol combination was followed by embolic microspheres. The percentage of drug administered was recorded, with confirmation of lipiodol deposition by noncontrast computed tomography (CT). Patients were admitted for 24–48 hours of observation, and discharged with antibiotics/analgesics/antiemetics as needed.	Follow-up: up until the last imaging date and for survival. Length of follow-up: *months (median and range)* *I: 21.0 (2.3-59.6)* *C: 15.7 (1.4-62.1)* Incomplete outcome data: Not reported.	Response rates (EASL): I: 20/23 (87%) C: 14/19 (74%) Median time to partial/complete response (EASL): I: 1.7 (1.6-3.4) months C: 1.4 (1.3-4.9) months Bridge to transplant (rate in listed patients): I: 13/15 (87%) C: 7/10 (70%) Median time to transplantation:	Conclusion authors: Intra-arterial embolotherapy is safe and has high antitumor activity. This study represents a real-world, comparative effectiveness analysis of Y90 and cTACE by ITT. In light of competing risks of liver transplantation and death, Y90 significantly increased TTP compared with cTACE in a randomized phase 2 setting, translating to significantly improved local tumor control that could reduce

	grant from the Society of Interventional Radiology Foundation. Three authors serve as advisors to BTG International.	- cardiac comorbidities - major surgery within the past 4 weeks - active infection N total at baseline: Intervention: 24 Control: 21 Important prognostic factors[2]: *age (median and 95% CI)* *I: 62 (58-65)* *C: 64 (62-70)* *Sex:* *I: 71% M* *C: 76% M* *BCLC stage:* *I: 75% A, 25% B* *C: 81% A, 19% B* Groups comparable at baseline? Yes				I: 8.8 (4.0-15.3) months C: 7.6 (3.0-17.3) months Overall survival (median, 95% CI): I: 18.6 (7.4-32.5) months C: 17.7 (8.3 - ?) months Time to progression (median): I: not reached (>26 months) C: 6.8 months *HR: 0.122; 95% CI: 0.027, 0.557; P = 0.007*	drop-out from transplant waitlists.
Dhondt, 2022 *TRACE study*	Type of study: RCT Setting and country: University Hospital, Ghent, Belgium Funding and conflicts of interest: the authors have nothing to disclose.	Inclusion criteria: - BCLC stage B HCC or BCLC stage A HCC not amenable to ablation, partial hepatectomy, or transplant - patients with ECOG performance status 1 and/or a Child-Pugh score of 7	TARE was performed with 90Y glass microspheres after angiographic tumor mapping with use of cone-beam CT and treatment simulation with	DEB-TACE was performed with doxorubicin DEBs sized 100–300 mm and 300–500 mm. The beads were delivered as selectively as possible, with a maximum doxorubicin dose of 150 mg per session. The embolization end point was reached when all the beads were administered, or earlier when sluggish flow was seen in the arterial tumor feeders.	Follow-up: 2 weeks following every treatment and every 3 months thereafter. Length of follow-up:	Objective response rate (ORR) treated area: I: 94% C: 100% Objective response rate (ORR) liver: I: 88%	Conclusion authors: Yttrium 90 (90Y) glass radioembolization, when compared with drug-eluting bead chemoembolization, resulted in superior tumor control and survival in participants with

		Exclusion criteria: - greater than 50% liver involvement - extrahepatic disease - invasion of the main, right, orleft portal vein - bilirubin over 34 mmol/L, or over 44 mmol/L in case of a single involved segment - Child-Pugh score higher than 7 N total at baseline: Intervention: 38 Control: 34 Important prognostic factors[2]: *age (median and IQR)* *I: 67 (63-72)* *C: 68 (61-71)* *Sex:* *I: 87% M* *C: 88% M* *BCLC stage:* *I: 18% A, 82% B* *C: 12% A, 88% B* Groups comparable at baseline? Yes	150-MBq technetium 99m macroaggregated albumin. Extrahepatic deposition of radioactivity was avoided and, if needed, the culprit vessels were coiled. Bilobar disease was treated in two separate sessions 30–45 days apart. If the tumor supply at cone-beam CT allowed for a more selective approach, segmental rather than lobar TARE was preferred. An absorbed dose of 120 Gy in the treated liver volume (except in specific cases) was aimed for.	If indicated, DEB-TACE was repeated with a maximum of three sessions per lesion and five sessions in total.	*months (median and IQR)* I: 28 (17-36) C: 15.6 (9-31) Loss-to-follow-up: Intervention: 0 (0.0%) Control: 0 (0.0%) Incomplete outcome data: Intervention: 1 (2.6%) Control: 1 (2.9%)	C: 87% Downstaging leading to transplantation: I: 10/38 (26%) C: 4/34 (12%) Overall survival (median): I: 30.2 months C: 15.6 months HR: *0.48; 95% CI: 0.28, 0.82; P = .006* PFS (median): I: 11.8 months C: 9.1 months HR: *0.40; 95% CI: 0.24, 0.67; P<.001*	nonsurgical Barcelona Clinic Liver Cancer (BCLC) stage A and B hepatocellular carcinoma (HCC). Because the safety profile was similar for both arms, 90Y glass radioembolization may become a legitimate local-regional treatment option in this patient population.

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 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 effectiveness of radioembolization versus transarterial chemoembolization in patients with hepatocellular carcinoma with BCLC stage 0-B?

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**

Kolligs, 2015	Definitely yes; Reason: Randomization with a stochastic balancing algorithm stratified by centre.	Probably no; Reason: Each site received a series of consecutively numbered sealed envelopes with the randomization result.	Definitely no; Reason: Open-label trial.	Definitely no; Reason: Only 18 of 28 complete cases were available for statistical analysis. Loss to follow-up was infrequent in intervention and control group and it is unclear whether imputation methods were used.	Probably no; Reason: Some of the secondary outcome measures in the trial register were not reported (e.g. pharmaco-economic assessment)	Definitely yes; Reason: No other problems noted.	HIGH
Pitton, 2015	Definitely yes; Reason: Treatment allocation was predetermined using a randomized block design.	Probably yes; Reason: An independent statistician performed the treatment allocation.	No information	Definitely yes; Reason: There was no loss to follow-up in the intervention and control group.	Definitely yes; Reason: All relevant outcomes were reported.	Definitely yes; Reason: No other problems noted.	LOW
Salem, 2016	No information	Definitely no; Reason: Concealment of allocation sequences was not described.	Probably yes; Reason: Scans were reviewed in a blinded manner (blinding of patients, healthcare providers, data collectors and analysts not reported).	Probably yes; Reason: The extent of censoring was high in both groups, but IPCW analyses were performed to address the potential issue of dependent censoring.	Definitely yes; Reason: All relevant outcomes were reported.	Probably no; Reason: The study was halted early because of slow accrual and competing studies.	Some concerns
Dhondt, 2022	Probably yes; Reason: Random treatment allocation was performed by minimization. Details of the minimization method are not provided.	Probably no; Reason: Concealment of allocation sequences was not described and could be an issue when using the	No information	Definitely yes; Reason: No participants were lost to follow-up. Data on α-fetoprotein was missing for one participant in each treatment arm.	Probably no; Reason: Some of the secondary outcome measures in the trial register were not reported (quality of life and	Probably yes; Reason: The study was terminated early: the statistical conditions at interim analysis were fulfilled to reject the null	Some concerns

		minimization method.			treatment-related costs).	hypothesis and request a halt of the study.	

Table of excluded studies

Reference	Reason for exclusion
Birgin E, Rasbach E, Seyfried S, Rathmann N, Diehl SJ, Schoenberg SO, Reissfelder C, Rahbari NN. Contralateral Liver Hypertrophy and Oncological Outcome Following Radioembolization with 90Y-Microspheres: A Systematic Review. Cancers (Basel). 2020 Jan 27;12(2):294. doi: 10.3390/cancers12020294. PMID: 32012709; PMCID: PMC7072354.	Wrong comparison (no comparison with TACE).
Bouattour, M., Assenat, E., Guiu, B., Alina, D. I., Pageaux, G. P., Sibert, A., ... & Vilgrain, V. (2017). Efficacy, tolerability and impact on quality of life of selective internal radiation therapy (with yttrium-90 resin microspheres) or sorafenib in patients with locally advanced hepatocellular carcinoma: The SARAH trial. Annals of Oncology, 28, iii150.	Abstract.
Chen, B. and Jia, Z. and Xie, S. and Wang, W. Yttrium- 90 radioembolization versus chemoembolization in the treatment of hepatocellular carcinoma: systematic review and meta- analysis. A series review of radioembolization with yttrium- 90 microsphere (part VI).	Full text in Chinese.
Chen X, Lai L, Ye J, Li L. Downstaging Therapies for Unresectable Hepatocellular Carcinoma Prior to Hepatic Resection: A Systematic Review and Meta-Analysis. Front Oncol. 2021 Nov 19;11:740762. doi: 10.3389/fonc.2021.740762. PMID: 34868936; PMCID: PMC8639517.	Wrong comparison (any treatment for HCC).
Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, Choo SP, Cheow PC, Chotipanich C, Lim K, Lesmana LA, Manuaba TW, Yoong BK, Raj A, Law CS, Cua IHY, Lobo RR, Teh CSC, Kim YH, Jong YW, Han HS, Bae SH, Yoon HK, Lee RC, Hung CF, Peng CY, Liang PC, Bartlett A, Kok KYY, Thng CH, Low AS, Goh ASW, Tay KH, Lo RHG, Goh BKP, Ng DCE, Lekurwale G, Liew WM, Gebski V, Mak KSW, Soo KC; Asia-Pacific Hepatocellular Carcinoma Trials Group. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol. 2018 Jul 1;36(19):1913-1921. doi: 10.1200/JCO.2017.76.0892. Epub 2018 Mar 2. PMID: 29498924.	Wrong intervention (TARE versus sorafenib).
Chow R, Simone CB 2nd, Jairam MP, Swaminath A, Boldt G, Lock M. Radiofrequency ablation versus radiation therapy versus transarterial chemoembolization versus yttrium 90 for local treatment of liver cancer - a systematic review and network meta-analysis of survival data. Acta Oncol. 2022 Apr;61(4):484-494. doi: 10.1080/0284186X.2021.2009563. Epub 2021 Nov 30. PMID: 34846988.	Wrong comparison (TARE versus other local treatment).
Das A, Gabr A, O'Brian DP, Riaz A, Desai K, Thornburg B, Kallini JR, Mouli S, Lewandowski RJ, Salem R. Contemporary Systematic Review of Health-Related Quality of Life Outcomes in Locoregional Therapies for Hepatocellular Carcinoma. J Vasc Interv Radiol. 2019 Dec;30(12):1924-1933.e2. doi: 10.1016/j.jvir.2019.07.020. Epub 2019 Nov 2. PMID: 31685362.	Wrong comparison (any treatment for HCC).
Facciorusso A, Paolillo R, Tartaglia N, Ramai D, Mohan BP, Cotsoglou C, Chandan S, Ambrosi A, Bargellini I, Renzulli M, Sacco R. Efficacy of combined transarterial radioembolization and sorafenib in the treatment of hepatocarcinoma: A meta-analysis. Dig Liver Dis. 2022 Mar;54(3):316-323. doi: 10.1016/j.dld.2021.06.003. Epub 2021 Jun 27. PMID: 34193367.	Wrong intervention (TARE +/- sorafenib).
Facciorusso A, Serviddio G, Muscatiello N. Transarterial radioembolization versus chemoembolization for hepatocarcinoma patients: A systematic review and meta-analysis. World J Hepatol. 2016 Jun 28;8(18):770-8. doi: 10.4254/wjh.v8.i18.770. PMID: 27366304; PMCID: PMC4921799.	Overlap with selected systematic review (Yang 2020).
Casadei Gardini A, Tamburini E, Iñarrairaegui M, Frassineti GL, Sangro B. Radioembolization versus chemoembolization for unresectable hepatocellular carcinoma: a meta-analysis of randomized trials. Onco Targets Ther. 2018 Oct 25;11:7315-7321. doi: 10.2147/OTT.S175715. PMID: 30498358; PMCID: PMC6207245.	Overlap with selected systematic review (Yang 2020).
Garin E, Tselikas L, Guiu B, Chalaye J, Edeline J, de Baere T, Assenat E, Tacher V, Robert C, Terroir-Cassou-Mounat M, Mariano-Goulart D, Amaddeo G, Palard X, Hollebecque A, Kafrouni M, Regnault H, Boudjema K, Grimaldi S, Fourcade M, Kobeiter H, Vibert E, Le Sourd S, Piron L, Sommacale D, Laffont S, Campillo-Gimenez B, Rolland Y; DOSISPHERE-01 Study Group. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol	Wrong intervention (standard versus personalized dosimetry).

Hepatol. 2021 Jan;6(1):17-29. doi: 10.1016/S2468-1253(20)30290-9. Epub 2020 Nov 7. PMID: 33166497.	
Jia Z, Jiang G, Tian F, Zhu C, Qin X. A systematic review on the safety and effectiveness of yttrium-90 radioembolization for hepatocellular carcinoma with portal vein tumor thrombosis. Saudi J Gastroenterol. 2016 Sep-Oct;22(5):353-359. doi: 10.4103/1319-3767.191139. PMID: 27748320; PMCID: PMC5051218.	Overlap with selected systematic review (Yang 2020).
Katsanos K, Kitrou P, Spiliopoulos S, Maroulis I, Petsas T, Karnabatidis D. Comparative effectiveness of different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments for unresectable hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. PLoS One. 2017 Sep 21;12(9):e0184597. doi: 10.1371/journal.pone.0184597. PMID: 28934265; PMCID: PMC5608206.	Wrong intervention (different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments).
Kim PH, Choi SH, Kim JH, Park SH. Comparison of Radioembolization and Sorafenib for the Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Systematic Review and Meta-Analysis of Safety and Efficacy. Korean J Radiol. 2019 Mar;20(3):385-398. doi: 10.3348/kjr.2018.0496. PMID: 30799569; PMCID: PMC6389804.	Wrong intervention (TARE versus sorafenib).
Kolligs FT, Bilbao JI, Jakobs T, Iñarrairaegui M, Nagel JM, Rodriguez M, Haug A, D'Avola D, op den Winkel M, Martinez-Cuesta A, Trumm C, Benito A, Tatsch K, Zech CJ, Hoffmann RT, Sangro B. Pilot randomized trial of selective internal radiation therapy versus. chemoembolization in unresectable hepatocellular carcinoma. Liver Int. 2015 Jun;35(6):1715-21. doi: 10.1111/liv.12750. Epub 2015 Jan 17. PMID: 25443863.	Included in selected systematic review (Yang 2020).
Kulik L, Vouche M, Koppe S, Lewandowski RJ, Mulcahy MF, Ganger D, Habib A, Karp J, Al-Saden P, Lacouture M, Cotliar J, Abecassis M, Baker T, Salem R. Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma. J Hepatol. 2014 Aug;61(2):309-17. doi: 10.1016/j.jhep.2014.03.023. Epub 2014 Mar 27. PMID: 24681342.	Wrong intervention (TARE +/- sorafenib).
Lemieux S, Buies A, F Turgeon A, Hallet J, Daigle G, Côté F, Provencher S. Effect of Yttrium-90 transarterial radioembolization in patients with non-surgical hepatocellular carcinoma: A systematic review and meta-analysis. PLoS One. 2021 Mar 4;16(3):e0247958. doi: 10.1371/journal.pone.0247958. PMID: 33662011; PMCID: PMC7932100.	Wrong comparison (TARE versus standard of care).
Liu Y, Wang Y, Guo X, He Y, Zhou J, Lv Q, Huang X, Li X. Comparative Effectiveness of Adjuvant Treatment for Resected Hepatocellular Carcinoma: A Systematic Review and Network Meta-Analysis. Front Oncol. 2021 Sep 2;11:709278. doi: 10.3389/fonc.2021.709278. PMID: 34540675; PMCID: PMC8445365.	Wrong comparison (adjuvant treatment for HCC, no TARE).
Lobo L, Yakoub D, Picado O, Ripat C, Pendola F, Sharma R, ElTawil R, Kwon D, Venkat S, Portelance L, Yechieli R. Unresectable Hepatocellular Carcinoma: Radioembolization Versus Chemoembolization: A Systematic Review and Meta-analysis. Cardiovasc Intervent Radiol. 2016 Nov;39(11):1580-1588. doi: 10.1007/s00270-016-1426-y. Epub 2016 Sep 1. Erratum in: Cardiovasc Intervent Radiol. 2017 May 25;: PMID: 27586657.	Overlap with selected systematic review (Yang 2020).
Ludwig JM, Zhang D, Xing M, Kim HS. Meta-analysis: adjusted indirect comparison of drug-eluting bead transarterial chemoembolization versus 90Y-radioembolization for hepatocellular carcinoma. Eur Radiol. 2017 May;27(5):2031-2041. doi: 10.1007/s00330-016-4548-3. Epub 2016 Aug 25. PMID: 27562480.	Overlap with selected systematic review (Yang 2020).
Palmer DH, Hawkins NS, Vilgrain V, Pereira H, Chatellier G, Ross PJ. Tumor burden and liver function in HCC patient selection for selective internal radiation therapy: SARAH post-hoc study. Future Oncol. 2020 Jan;16(1):4315-4325. doi: 10.2217/fon-2019-0658. Epub 2019 Dec 4. PMID: 31797680.	Wrong intervention (TARE versus sorafenib, subanalysis RCT).
Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: A systematic review and pooled analysis. Liver Transpl. 2015 Sep;21(9):1142-52. doi: 10.1002/lt.24169. Erratum in: Liver Transpl. 2016 Jan;22(1):138. PMID: 25981135.	Wrong intervention (downstaging techniques).
Pereira H, Bouattour M, Dioguardi Burgio M, Assenat E, Grégory J, Bronowicki JP, Chatellier G, Vilgrain V; SARAH Trial Group. Health-related quality of life in locally advanced hepatocellular carcinoma treated by either	Wrong intervention (TARE versus sorafenib, subanalysis RCT).

radioembolisation or sorafenib (SARAH trial). Eur J Cancer. 2021 Sep;154:46-56. doi: 10.1016/j.ejca.2021.05.032. Epub 2021 Jul 6. PMID: 34243077.	
Pitton MB, Kloeckner R, Ruckes C, Wirth GM, Eichhorn W, Wörns MA, Weinmann A, Schreckenberger M, Galle PR, Otto G, Dueber C. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol. 2015 Apr;38(2):352-60. doi: 10.1007/s00270-014-1012-0. Epub 2014 Nov 7. PMID: 25373796; PMCID: PMC4355443.	Included in selected systematic review (Yang 2020).
Pollock RF, Brennan VK, Shergill S, Colaone F. A systematic literature review and network meta-analysis of first-line treatments for unresectable hepatocellular carcinoma based on data from randomized controlled trials. Expert Rev Anticancer Ther. 2021 Mar;21(3):341-349. doi: 10.1080/14737140.2021.1842204. Epub 2021 Feb 10. PMID: 33131346.	Wrong intervention (TARE versus systemic therapy).
Ren, N., Qin, S., Ding, L., Jia, E., & Xue, J. (2020). Comparison of Transarterial Y90 Radioembolization and Conventional Transarterial Chemoembolization in Hepatocarcinoma Patients: A Meta-analysis. Indian Journal of Pharmaceutical Sciences, 76-81.	Systematic review without RCTs.
Ricke J, Bulla K, Kolligs F, Peck-Radosavljevic M, Reimer P, Sangro B, Schott E, Schütte K, Verslype C, Walecki J, Malfertheiner P; SORAMIC study group. Safety and toxicity of radioembolization plus Sorafenib in advanced hepatocellular carcinoma: analysis of the European multicentre trial SORAMIC. Liver Int. 2015 Feb;35(2):620-6. doi: 10.1111/liv.12622. Epub 2014 Jul 8. PMID: 24930619.	Wrong intervention (TARE +/- sorafenib).
Ricke J, Klümpen HJ, Amthauer H, Bargellini I, Bartenstein P, de Toni EN, Gasbarrini A, Pech M, Peck-Radosavljevic M, Popovič P, Rosmorduc O, Schott E, Seidensticker M, Verslype C, Sangro B, Malfertheiner P. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. J Hepatol. 2019 Dec;71(6):1164-1174. doi: 10.1016/j.jhep.2019.08.006. Epub 2019 Aug 14. PMID: 31421157.	Wrong intervention (TARE +/- sorafenib).
Rim CH, Kim CY, Yang DS, Yoon WS. Comparison of radiation therapy modalities for hepatocellular carcinoma with portal vein thrombosis: A meta-analysis and systematic review. Radiother Oncol. 2018 Oct;129(1):112-122. doi: 10.1016/j.radonc.2017.11.013. Epub 2017 Dec 9. PMID: 29233562.	Wrong comparison (TARE versus radiotherapy in portal vein thrombosis).
Rognoni C, Ciani O, Sommariva S, Facciorusso A, Tarricone R, Bhoori S, Mazzaferro V. Trans-arterial radioembolization in intermediate-advanced hepatocellular carcinoma: systematic review and meta-analyses. Oncotarget. 2016 Nov 1;7(44):72343-72355. doi: 10.18632/oncotarget.11644. PMID: 27579537; PMCID: PMC5342166.	Overlap with selected systematic review (Yang 2020).
Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, Mulcahy MF, Baker T, Abecassis M, Miller FH, Yaghmai V, Sato K, Desai K, Thornburg B, Benson AB, Rademaker A, Ganger D, Kulik L, Lewandowski RJ. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology. 2016 Dec;151(6):1155-1163.e2. doi: 10.1053/j.gastro.2016.08.029. Epub 2016 Aug 27. PMID: 27575820; PMCID: PMC5124387.	Included in selected systematic review (Yang 2020).
Schütte K, Schinner R, Fabritius MP, Möller M, Kuhl C, Iezzi R, Öcal O, Pech M, Peynircioglu B, Seidensticker M, Sharma R, Palmer D, Bronowicki JP, Reimer P, Malfertheiner P, Ricke J. Impact of Extrahepatic Metastases on Overall Survival in Patients with Advanced Liver Dominant Hepatocellular Carcinoma: A Subanalysis of the SORAMIC Trial. Liver Cancer. 2020 Dec;9(6):771-786. doi: 10.1159/000510798. Epub 2020 Nov 11. PMID: 33442545; PMCID: PMC7768116.	Wrong intervention (TARE +/- sorafenib, subanalysis RCT).
Teo JY, Allen JC Jr, Ng DC, Choo SP, Tai DW, Chang JP, Cheah FK, Chow PK, Goh BK. A systematic review of contralateral liver lobe hypertrophy after unilobar selective internal radiation therapy with Y90. HPB (Oxford). 2016 Jan;18(1):7-12. doi: 10.1016/j.hpb.2015.07.002. Epub 2015 Dec 11. PMID: 26776845; PMCID: PMC4750235.	Wrong comparison (no comparison with TACE).
Venerito M, Pech M, Canbay A, Donghia R, Guerra V, Chatellier G, Pereira H, Gandhi M, Malfertheiner P, Chow PKH, Vilgrain V, Ricke J, Leandro G. NEMESIS: Noninferiority, Individual-Patient Metaanalysis of Selective Internal	Wrong intervention (TARE versus systemic therapy).

Radiation Therapy with 90Y Resin Microspheres Versus Sorafenib in Advanced Hepatocellular Carcinoma. J Nucl Med. 2020 Dec;61(12):1736-1742. doi: 10.2967/jnumed.120.242933. Epub 2020 May 1. PMID: 32358087.	
Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, Sibert A, Bouattour M, Lebtahi R, Allaham W, Barraud H, Laurent V, Mathias E, Bronowicki JP, Tasu JP, Perdrisot R, Silvain C, Gerolami R, Mundler O, Seitz JF, Vidal V, Aubé C, Oberti F, Couturier O, Brenot-Rossi I, Raoul JL, Sarran A, Costentin C, Itti E, Luciani A, Adam R, Lewin M, Samuel D, Ronot M, Dinut A, Castera L, Chatellier G; SARAH Trial Group. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017 Dec;18(12):1624-1636. doi: 10.1016/S1470-2045(17)30683-6. Epub 2017 Oct 26. PMID: 29107679.	Wrong intervention (TARE versus sorafenib).
Vogel A, Rimassa L, Sun HC, Abou-Alfa GK, El-Khoueiry A, Pinato DJ, Sanchez Alvarez J, Daigl M, Orfanos P, Leibfried M, Blanchet Zumofen MH, Gaillard VE, Merle P. Comparative Efficacy of Atezolizumab plus Bevacizumab and Other Treatment Options for Patients with Unresectable Hepatocellular Carcinoma: A Network Meta-Analysis. Liver Cancer. 2021 Jun;10(3):240-248. doi: 10.1159/000515302. Epub 2021 May 6. PMID: 34239810; PMCID: PMC8237801.	Wrong intervention (atezolizumab + bevacizumab).
Walton M, Wade R, Claxton L, Sharif-Hurst S, Harden M, Patel J, Rowe I, Hodgson R, Eastwood A. Selective internal radiation therapies for unresectable early-, intermediate- or advanced-stage hepatocellular carcinoma: systematic review, network meta-analysis and economic evaluation. Health Technol Assess. 2020 Sep;24(48):1-264. doi: 10.3310/hta24480. PMID: 33001024; PMCID: PMC7569721.	Wrong intervention (TARE versus systemic therapy).
Wang H, Wang H, Yu Z, Liu H. Alternative treatment strategies to sorafenib in patients with advanced hepatocellular carcinoma: a meta-analysis of randomized Phase III trials. Onco Targets Ther. 2018 Aug 27;11:5195-5201. doi: 10.2147/OTT.S171918. PMID: 30214225; PMCID: PMC6118246.	Wrong intervention (TARE versus systemic therapy).
Yang Y, Si T. Yttrium-90 transarterial radioembolization versus conventional transarterial chemoembolization for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Cancer Biol Med. 2018 Aug;15(3):299-310. doi: 10.20892/j.issn.2095-3941.2017.0177. PMID: 30197797; PMCID: PMC6121048.	Overlap with selected systematic review (Yang 2020).
Zhang Y, Li Y, Ji H, Zhao X, Lu H. Transarterial Y90 radioembolization versus chemoembolization for patients with hepatocellular carcinoma: A meta-analysis. Biosci Trends. 2015 Oct;9(5):289-98. doi: 10.5582/bst.2015.01089. PMID: 26559021.	Overlap with selected systematic review (Yang 2020).
Min, Z. H. U., Liang, Y. U. E., Yi, L. U., & WANG, S. M. (2019). Efficacy and safety of yttrium-90 radioembolization for unresectable hepatocellular carcinoma: A systematic review and meta analysis. Medical Journal of Chinese People's Liberation Army, 44(10), 876-880.	Full text in Chinese.
Zou J, Zhu W, Meng H, Luo P, Zhang J. Efficacy and safety of selective internal radiotherapy versus sorafenib for intermediate-locally advanced hepatocellular carcinoma: a systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol. 2019 Mar;13(3):271-279. doi: 10.1080/17474124.2019.1570135. Epub 2019 Jan 25. PMID: 30791765.	Wrong intervention (TARE versus systemic therapy).

Literature search strategy

Algemene informatie

Richtlijn: NVMDL hepatocellulair carcinoom	
Uitgangsvraag: UV 7.1 Is radioembolisatie beter dan 'standard of care' zoals gedefinieerd in bovenstaand BCLC schema?	
Database(s): Ovid/Medline, Embase	Datum: 8-2-2022
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: Hepatocellulair carcinoom EN radioembolisatie Met SR en RCT worden 7 van de 15 sleutelartikelen gevonden. De overige artikelen worden gevonden met het observationeel filter, muv 1 artikel dat verkeerd is geïndexeerd. Elsevier is op de hoogte gesteld. Totaal gevonden in 1`database: 155 SR, 141 RCT, 892 observationele studies. Met de adviseur is afgestemd dat alleen de SRs en RCTs in Rayyan worden aangeboden	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 8 februari 2022 met relevante zoektermen gezocht naar systematische reviews en RCTs over de vraag of radioembolisatie beter is dan standaard zorg. De literatuurzoekactie leverde 340 unieke treffers op.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	182	98	202
RCTs	166	100	138
Observationele studies			
Overig			
Totaal			340

5

Zoekstrategie

Embase

No.	Query	Results
#29	#24 NOT #28	**1**
#28	#4 AND #24 sleutelartikelen gevonden	**14**
#27	#24 NOT #26	**8**
#26	#24 AND #25	**7**
#25	#7 OR #8	**254**
#24	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	**15**
#23	chow AND 2018 AND internal AND radiation AND therapy AND hepatocellular AND sorafenib AND sirvenib:ti AND patients:ti	**1**
#22	. AND impact AND of AND combined AND selective AND internal AND radiation AND therapy AND sorafenib AND on AND survival AND in AND advanced AND hepatocellular AND carcinoma AND ricke	**1**
#21	venerito AND 2020 AND microspheres	**1**

#20	efficacy AND safety AND of AND selective AND internal AND radiotherapy AND 'yttrium 90' AND resin AND microspheres AND compared AND with AND sorafenib AND in AND locally AND advanced AND inoperable AND hepatocellular AND carcinoma AND vilgrain NOT economic:ti	**1**
#19	personalized AND dosimetry AND intensification AND using AND glass AND microsphere AND radioembolization AND induces AND prolonged AND overall AND survival AND in AND hepatocellular AND carcinoma AND patients AND with AND portal AND vein AND thrombosis AND garin	**1**
#18	transarterial AND radioembolization AND versus AND systemic AND treatment AND for AND hepatocellular AND carcinoma AND with AND macrovascular AND invasion AND ahn	**1**
#17	locally AND advanced AND hepatocellular AND carcinoma AND with AND portal AND vein AND thrombosis AND 2018 AND abouchaleh	**1**
#16	'yttrium 90' AND radioembolization AND for AND 'intermediate advanced' AND hepatocellular AND carcinoma AND a AND phase AND 2 AND study AND mazzaferro AND 2013 NOT microspheres:ti NOT internal:ti	**1**
#15	institutional AND decision AND to AND adopt AND y90 AND as AND primary AND treatment AND for AND hepatocellular AND carcinoma AND informed AND by AND a AND '1,000 patient' AND '15 year' AND experience AND salem	**1**
#14	. AND a AND comparative AND study AND of AND portal AND vein AND embolization AND versus AND radiation AND lobectomy AND with AND 'yttrium 90' AND micropheres AND in AND preparation AND liver AND resection AND for AND initially AND unresectable AND hepatocellular AND carcinoma AND bekki	**1**
#13	'yttrium 90' AND radioembolization AND versus AND segmental AND chemoembolization AND for AND localized AND hepatocellular AND carcinoma AND padia AND 2017	**1**
#12	correlation AND of AND 'y90 absorbed' AND radiation AND dose AND to AND pathological AND necrosis AND in AND hepatocellular AND carcinoma AND gabr AND 2021	**1**
#11	liver AND transplantation AND following AND 'yttrium 90' AND radioembolization AND gabr AND 2021	**1**
#10	'yttrium 90' AND radioembolization AND for AND the AND treatment AND of AND solitary AND sale m AND 2021 AND unresectable NOT gupta	**1**
#9	personalised AND versus AND standard AND dosimetry AND approach AND of AND selective AND internal AND radiation AND therapy AND in AND patients AND with AND locally AND advanced AND hepatocellular AND carcinoma	**1**
#8	#4 AND #6 RCT	**166**
#7	#4 AND #5 SR	**182**
#6	'randomized controlled trial'/exp OR random*:ti,ab OR (((pragmatic OR practical) NEAR/1 'clinical trial*'):ti,ab) OR (('non	**1869324**

	inferiority' OR noninferiority OR superiority OR equivalence) NEAR/3 trial*):ti,ab) OR rct:ti,ab,kw	
#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)	**1918**
#3	#1 AND #2	**3314**
#2	'radioembolization'/exp OR 'brachytherapy'/de OR 'selective internal radiation therapy'/de OR 'radioemboli?at*':ti,ab,kw OR 'radio emboli?at*':ti,ab,kw OR tare:ti,ab,kw OR 'selective internal radiation therap*':ti,ab,kw OR sirt:ti,ab,kw OR brachytherap*:ti,ab,kw	**54174**
#1	'liver cell carcinoma'/exp OR (((hepat* OR liver) NEAR/3 carcinom*):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw	**231607**

Ovid/Medline

#	Searches	Results
10	9 not 8 RCT	100
9	5 and 6	138
8	5 and 7 SR	98
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)	546472

	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/))	
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.) not (animals/ not humans/)	1350790
5	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1396
4	limit 3 to yr="2000 -Current"	1500
3	1 and 2	1550
2	Brachytherapy/ or radioemboli?ation.ti,ab,kf. or radio emboli?ation.ti,ab,kf. or tare.ti,ab,kf. or selective internal radiation therap*.ti,ab,kf. or brachytherap*.ti,ab,kf. or sirt.ti,ab,kf.	30602
1	Carcinoma, Hepatocellular/ or (hepat* adj3 carcinom*).ti,ab,kf. or hepatocarcinom*.ti,ab,kf. or hepatoma.ti,ab,kf. or (liver adj3 primary).ti,ab,kf.	160661

Module 7-2 Hepatocellulair carcinoom – Combinatiebehandeling TACE en ablatie

Uitgangsvraag

Wat is de plaatsbepaling van een combinatiebehandeling van TACE en ablatie?

Inleiding

Voor een solitair hepatocellulair carcinoom (HCC) tot 2 cm is de effectiviteit van ablatie vergelijkbaar met die van resectie. Bij grotere tumoren wordt doorgaans de voorkeur gegeven aan resectie. In het algemeen wordt de kans op een lokaal recidief na ablatie groter geacht dan na resectie bij tumoren groter dan 2 tot 3 cm. De resultaten van ablatie zijn in voorbije jaren evenwel steeds beter geworden, dankzij verbeteringen in ablatiesytemen en naaldpositionering. Daarbij is een aanzienlijk deel van de patiënten met een tumor >2 cm geen kandidaat voor resectie, ten gevolge van cirrose met portale hypertensie, hoge leeftijd, co-morbiditeit en/of een ongunstige ligging van de tumor.

Om de effectiviteit van ablatie bij grotere tumoren te vergroten, zijn er diverse trials verricht waarbij ablatie is gecombineerd met transarteriële chemoembolisatie (TACE). De combinatie met TACE is mogelijk effectiever dan ablatie alleen.

Search and select

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

What is the effectiveness of the combination of transarterial chemoembolization (TACE) and ablation compared to TACE or ablation alone in patients with early stage HCC (BCLC A)?

P: patients with a hepatocellular carcinoma (early-stage HCC/BCLC A, >2 cm);
I: combination therapy of TACE and ablation;
C: TACE or ablation alone;
O: overall survival, disease-free survival, local recurrence, quality of life, bridge to transplant, local tumor control, complications.

<u>Relevant outcome measures</u>

The guideline development group considered overall survival and disease-free survival as critical outcome measures for decision making; and local recurrence, quality of life, bridge to transplant, local tumor control and complications as important outcome measures for decision making.

The working group defined the outcome measures as follows:

- Overall survival: Time to death from any cause with a minimum follow-up of one year.
- Disease-free survival: Time from randomization or initiation of treatment to recurrence of tumor or death from any cause.
- Local tumor control: Lack of tumor progression (complete response + partial response + stable disease).
- Complications: Adverse events following treatment (grade 3 and higher or serious/major adverse events).

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

- Overall survival: Absolute difference >5% or absolute difference >3% and Risk Ratio (RR) <0.7.

- Disease-free survival: Absolute difference >5% or absolute difference >3% and Risk Ratio (RR) <0.7.
- Local tumor control: Absolute difference >5%.
- Complications: Absolute difference >3% for lethal complications, or >10% for serious complications.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2010 until 03-02-2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 515 hits. Studies were selected based on the following criteria:

- Systematic reviews or randomized controlled trials.
- full-text English language publication.
- complying with the PICO criteria.

Fifty-seven studies were initially selected based on title and abstract screening. After reading the full text, 56 studies were excluded (see the table with reasons for exclusion under the tab Methods). One systematic review comparing radioembolization to chemoembolization was selected. One additional RCT was included.

Results

One systematic review was selected, of which seven RCTs were extracted. One additional RCT was included, resulting in eight studies for 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

Li (2021) conducted a systematic review on hyperthermia ablation (HA) combined with TACE versus monotherapy for the treatment of hepatocellular carcinoma. The effects of HA (radiofrequency ablation (RFA)/microwave ablation (MWA)) combined with TACE and monotherapy (HA or TACE) on overall survival, adverse effects and complications were evaluated. Multiple databases (Cochrane Library, Web of Science, PubMed, Embase, and Scopus) were searched up to May 2021. Thirty-six studies were included, of which 15 (randomized) controlled trials (RCTs). Seven RCTs (**Liu, 2011; Liu, 2014; Morimoto, 2010; Peng, 2012; Peng, 2013; Sheta, 2016; Zaitoun, 2021**) were included in this literature analysis. The other RCTs were excluded because of publication date <2010, no randomization, double cohorts or wrong outcome measures.

Liu (2011) evaluated the efficacy and safety of TACE followed by MWA compared to TACE alone for unresectable large-sized (>5 cm) hepatocellular carcinoma. A total of 16 patients was randomized into the combination group (mean age 52.1±14.5; 88% male) and 18 into the TACE group (mean age 51.9±13.6; 83% male). The study had an open-label design.

Liu (2014) evaluated the efficacy of TACE followed by RFA compared to TACE alone for advanced hepatocellular carcinoma (>3 cm). A total of 45 patients was randomized into the combination group (age, range 45 to 75; 80% male) and 43 into the TACE group (age, range 44-78; 79% male). The study had an open-label design, and no information was given on randomization and allocation concealment methods.

Morimoto (2010) evaluated the efficacy of TACE followed by RFA compared to RFA alone for intermediate-sized (3.1 to 5.0 cm) hepatocellular carcinoma. A total of 19 patients was randomized into the combination group (mean age 70, range 57 to 78; 79% male) and 18 nto the RFA group (mean age 73, range 48 to 84; 67% male). The study had an open-label design.

Peng (2012) evaluated the efficacy of TACE followed by RFA compared to RFA alone for recurrent hepatocellular carcinoma (≤5 cm). A total of 69 patients was randomized into the combination group (mean age 57.5±10.0; 86% male) and 70 into the RFA group (mean age 55.1±9.5; 79% male). The study had an open-label design.

Peng (2013) evaluated the efficacy of TACE followed by RFA compared to RFA alone for hepatocellular carcinoma (≤7 cm). A total of 94 patients was randomized into the combination group (mean age 53.3±11.0; 80% male) and 95 into the RFA group (mean age 55.3±13.3; 75% male). The study had an open-label design.

Sheta (2016) compared combination treatments (RFA or MWA followed by TACE) with TACE alone for non-resectable single-lesion hepatocellular carcinoma (>4 cm). A total of 50 patients was divided into three groups: a combination group of TACE and RFA (n=20), a combination group of TACE and MWA (n=10) and a TACE group (n=20). Baseline characteristics such as age and sex were not described. The study had an open-label design, and no information was given on randomization and allocation concealment methods.

Zaitoun (2021) evaluated the efficacy and safety of TACE followed by MWA compared to TACE or MWA alone for treatment of hepatocellular carcinoma (3-5 cm). A total of 89 patients was randomized into the combination group (mean age 52.1±9.5; 58% male), 84 into the TACE group (51.3±9.2; 62% male) and 92 into the MWA group (mean age 53.8±10.3; 54% male). The study had an open-label design, and it was unknown in which group the lost-to-follow-up (n=12) occurred.

One additional RCT was published after the search date of the systematic review by Li (2021).

Zhang (2021) evaluated the long-term outcomes and safety of TACE followed by RFA compared to RFA alone for early hepatocellular carcinoma (≤ 7 cm). A total of 94 patients was randomized into the combination group (mean age 53.3±11.0; 80% male) and 95 into the RFA group (mean age 55.3±13.3; 75% male). The study had an open-label design. The study was based on long-term follow-up of patients who were recruited into the previously reported RCT by Peng (2013).

Results

Overall survival (critical)

Six studies reported overall survival (OS). The results are split by type of monotherapy: two studies compared the OS in a combination group and a TACE group (figure 7.2.1) and four studies compared the OS in a combination group and an ablation group (figure 7.2.2).

All results for the OS on different time-points (1-, 2-, 3-, 5- and 7-year) favored the combination group, both in comparison with TACE and ablation alone.

Results were pooled for the 1-year OS and 3-year OS for the combination versus ablation. For the 1-year OS, the pooled RR was 0.33 (95% CI: 0.16 to 0.66). For the 3-year OS, the pooled RR was 0.65 (0.52 to 0.82). These differences are clinically relevant.

The study population of Zhang (2021) is equal to the population of Peng (2013), so the overall survival results of Peng (2013) were not meta-analyzed.

Figure 7.2.1. Outcome 1-, 2- and 3-year overall survival with TACE+ablation versus TACE

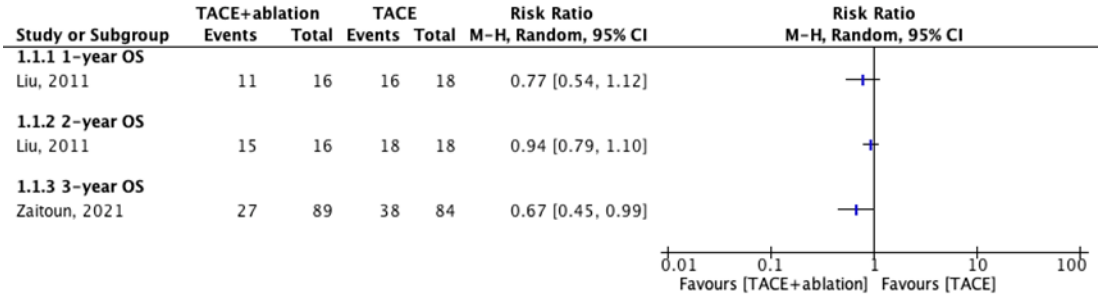
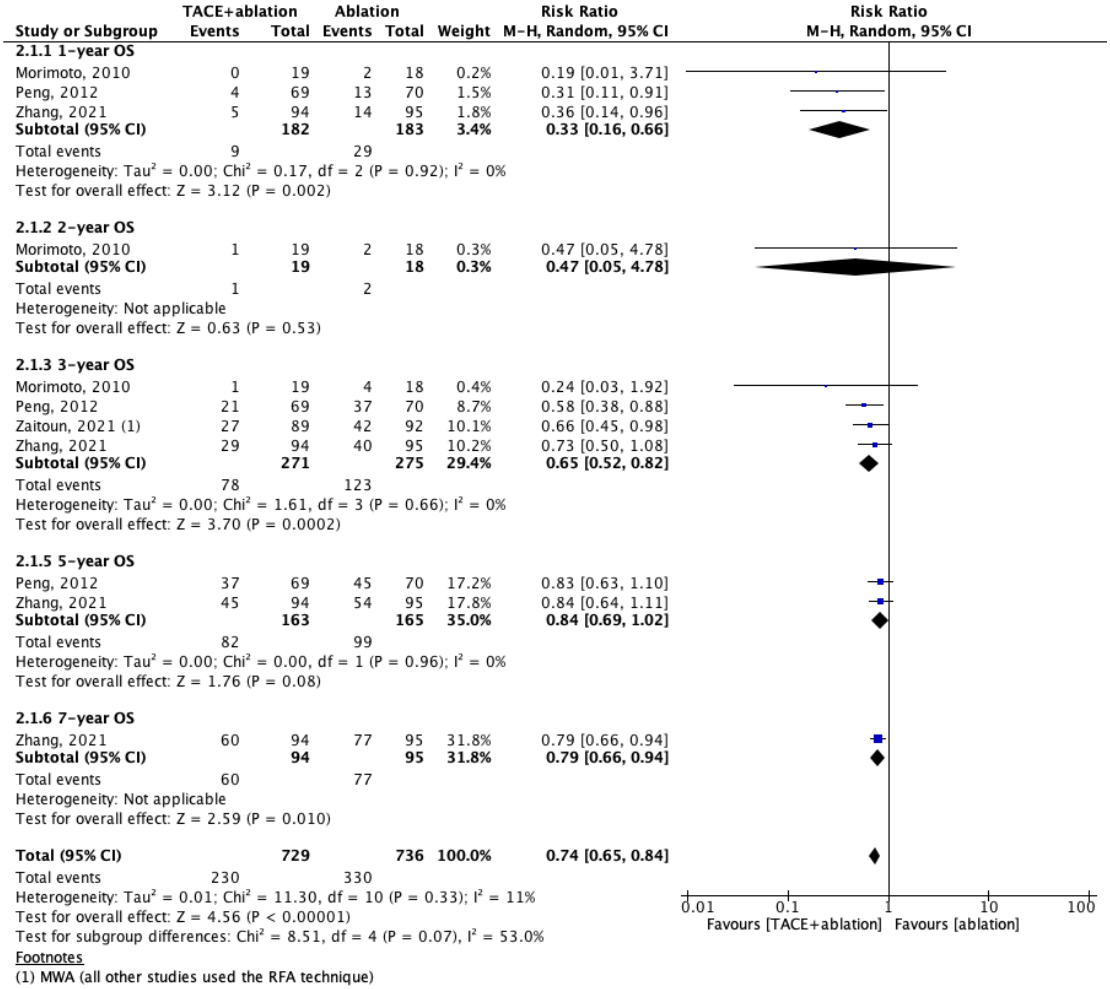


Figure 7.2.2. Outcome 1-, 2-, 3-, 5- and 7-year overall survival with TACE+ablation versus ablation



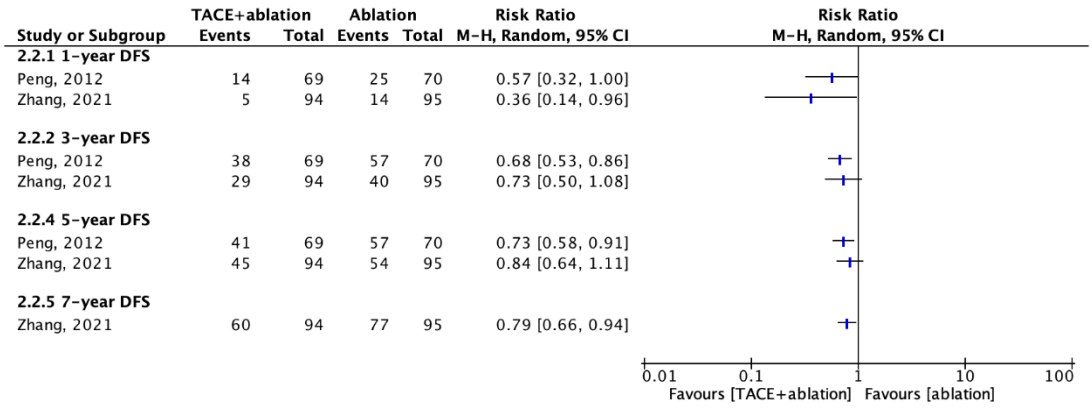
Z: p-value of pooled effect; df: degrees of freedom, I2: statistical heterogeneity, CI: confidence interval

Disease-free survival (critical)
Three studies reported disease-free survival (DFS). These studies compared the DFS in a combination group and an ablation group (figure 7.2.3). None of the included studies compared the DFS in a combination group and a TACE group.

All results for the DFS on different time-points (1-, 3-, 5-, 7-year) favored the combination group.

The study population of Zhang (2021) is equal to the population of Peng (2013), so the disease-free survival results of Peng (2013) were not meta-analyzed.

Figure 7.2.3. Outcome 1-, 3-, 5-, and 7-year disease-free survival with TACE+ablation versus ablation



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

Local tumor control (important)
Local tumor control was not defined as such by the included studies.

However, one study reported the (local) tumor progression.

Morimoto (2010) reported a local tumor progression rate of 6% in the combination group and a rate of 39% in the ablation group after 1, 2 and 3 years. The risk difference is 33%, which is clinically relevant.

Peng (2012), Peng (2013) and Zhang (2021) reported the number of patients that died because of (local) tumor progression in the follow-up.

Peng (2012) reported that local tumor progression was the cause of death in 28.9% of the patients in the combination group (21/69) and 32.8% in the ablation group (23/70).

Peng (2013) reported that tumor progression was the cause of death in 22.3% of the patients in the combination group (21/94) and 44.2% of the patients in the ablation group (42/95). In the follow-up results of this study (Zhang, 2021), 47.9% of the patients in the combination group (45/94) and 72.6% of the patients in the ablation group (69/95) had died because of tumor progression.

Complications (important)
Major complications were reported by six studies.

Morimoto (2010) reported no major complications in both the combination group and the ablation group.

Peng (2012) reported major complications in 2.9% of the patients in the combination group (2/69, moderate ascites/liver failure) and in 2.8% of the patients in the ablation group (2/70, severe ascites/persistent jaundice). Grade 3 pain was observed in 1 patient in the combination group (1.4%) and 1 patient in the ablation group (1.4%). Grade 3 vomiting was observed in 1 patient in the combination group (1.4%). These differences are not clinically relevant.

Peng (2013) reported grade 3 pain in 2.1% of the patients in the combination group (2/94) and in 1.1% of the patients in the ablation group (1/95). Grade 3 vomiting was observed in 1 patient in the ablation group (1.1%). These differences are not clinically relevant.

Liu (2011) reported no major complications in both the combination group and the ablation group.

Sheta (2016) reported major complications in 10% of the patients in the TACE+RFA combination group (2/20, ascites/tumor rupture/renal impairment), in 10% of the patients in the TACE+MWA combination group (1/10, decompensation/ascites) and in 40% of the patients in the TACE group (8/20, decompensation/ascites/tumor rupture/renal impairment). These differences are clinically relevant.

Zaitoun (2021) reported major complications in 1.1% of the patients in the combination group (1/89, severe hepatic dysfunction), in 2.2% of the patients in the ablation group (2/92, tumor seeding) and in 3.6% of the patients in the TACE group (3.84, severe hepatic dysfunction). These differences are not clinically relevant.

<u>Level of evidence of the literature</u>
The level of evidence of randomized controlled trials is considered high according to the GRADE methodology. Therefore, the level of evidence of these cohort studies starts at high GRADE.

Overall survival
The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of study limitations (risk of bias, -1 (see RoB assessment)) and indirectness (-1; different populations and use of different treatment regimens in the intervention and control group). The level of evidence was therefore graded as low.

Disease-free survival
The level of evidence regarding the outcome measure **disease-free survival** was downgraded by two levels because of study limitations (risk of bias, -1 (see RoB assessment)) and low number of patients (imprecision, -1). The level of evidence was therefore graded as low.

Local tumor control
The level of evidence regarding the outcome measure **local tumor control** was downgraded by three levels because of study limitations (risk of bias, -1 (see RoB assessment)), indirectness (-1; different populations and use of different treatment regimens in the intervention and control group) and low number of patients (imprecision, -1). 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 (risk of bias, -1 (see RoB assessment)), indirectness (-1; different populations and use of different treatment regimens in the intervention and control group) and low number of patients (imprecision, -1). The level of evidence was therefore graded as very low.

Conclusions

Overall survival

Low GRADE	Combination therapy of TACE and ablation may result in a higher **overall survival** than TACE or ablation alone in patients with early-stage hepatocellular carcinoma, but the evidence is uncertain. *Sources: (Liu, 2011; Morimoto, 2010; Peng, 2012; Peng, 2013; Zaitoun, 2021; Zhang, 2021)*

Disease-free survival

Low GRADE	Combination therapy of TACE and ablation may result in a higher **disease-free survival** than ablation alone in patients with early-stage hepatocellular carcinoma, but the evidence is uncertain. *Sources: (Peng, 2012; Peng, 2013; Zhang, 2021)*

Local tumor control

Very low GRADE	Combination therapy of TACE and ablation may result in a higher **local tumor control** than TACE or ablation alone in patients with early-stage hepatocellular carcinoma, but the evidence is very uncertain. *Sources: (Morimoto, 2010)*

Complications

Very low GRADE	The evidence is very uncertain about the effect of combination therapy of TACE and ablation on **complications** compared with the effect of TACE or ablation alone in patients with early-stage hepatocellular carcinoma. *Sources: (Liu, 2011; Morimoto, 2010; Peng, 2012; Peng, 2013; Sheta, 2016; Zaitoun, 2021)*

Overwegingen – van bewijs naar aanbeveling

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

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen een combinatiebehandeling met transarteriële radio-embolisatie (TACE) en ablatie in vergelijking met TACE of ablatie alleen bij patiënten met early-stage hepatocellulair carcinoom. Er werden acht gerandomiseerde gecontroleerde studies (RCTs) geselecteerd en uitgewerkt (Liu, 2011; Liu, 2014; Morimoto, 2010; Peng, 2012; Peng, 2013; Sheta, 2016; Zaitoun, 2021; Zhang, 2021).

Bij de meeste studies waren de lesies tussen de 3 en 5 cm. Enkele studies keken (ook) naar grotere lesies. Conclusies en aanbevelingen binnen deze module beperken zich tot lesies tussen de 3 en 5 cm, omdat ablatie in de regel in Nederland niet wordt toegepast bij lesies boven de 5 cm. Het aantal patiënten in de studies met grotere lesies is zeer beperkt.

Er werden alleen RCTs geïncludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. De geïncludeerde studies hadden in wisselende mate methodologische beperkingen (risk of bias). Er was in sommige studies een risico op bias door onder andere ontoereikende documentatie, loss of follow-up en blindering. Daarnaast waren de studiebevindingen soms moeilijk met elkaar te vergelijken omdat de controle interventies en de populaties van elkaar verschilden (indirectness) en waren er meerdere studies met een relatief kleine populatie en mede hierdoor een grote spreiding van de puntschatter van de uitkomstmaat (imprecision), waardoor de kwaliteit van dit bewijs ook naar beneden werd bijgesteld. De bewijskracht van de literatuur werd voor zowel de cruciale als belangrijke uitkomstmaten, door bovenstaande bevindingen gegradeerd als 'laag' of 'zeer laag'.

De geïncludeerde studies zijn allen uitgevoerd in niet-westerse populaties en het ontbreekt aan studies die de resultaten bevestigen in een overwegend kaukasische patiëntenpopulatie met een andere etiologie voor cirrose en HCC. Daarbij zijn de meeste studies gedateerd en uitgevoerd met RFA. In recente jaren zijn ablatiesystemen verbeterd en is in veel centra RFA (groten)deels vervangen door MWA. Bovendien zijn recidiefpercentages hedentendage ook bij grotere lesies (3 tot 5 cm) laag wanneer gebruik gemaakt wordt van geavanceerde planningssoftware, naaldpositioneringssystemen, multipele naalden en/of confirmatiesoftware (Beermann, 2020; Laimer, 2020; Schullian, 2022). Wanneer gebruik gemaakt wordt van deze technologieën is er grotere zekerheid op het behalen van technisch succes, i.e. complete tumorablatie met een adequate marge, en is het onzeker of (neo)adjuvante TACE nog van meerwaarde is (Laimer, 2020; Rai, 2023). Bij patiënten bij wie er op voorhand twijfel is of er adequate marges kunnen worden behaald door bijvoorbeeld een centrale ligging of nabijgelegen groot bloedvat, kan worden overwogen neoadjuvant TACE te verrichten met het doel de lesie in grootte te doen afnemen en zo wel adequate marges te verkrijgen.

Tussen de verschillende studies waren er aanzienlijke verschillen in gebruikte materialen en het interval tussen TACE en ablatie. Er is op dit moment geen eenduidige aanbeveling te geven welke technieken de voorkeur genieten (RFA of MWA, conventionele TACE of drug-eluting bead TACE) of het interval dat dient te worden aangehouden tussen TACE en ablatie (Hendriks, 2021). In zeven van de acht geïncludeerde studies werd TACE verricht voorafgaand aan de ablatie.

In deze module is combinatietherapie met TACE en ablatie onderzocht bij de behandeling van één en dezelfde lesie. Er is geen analyse verricht naar de combinatie behandeling bij verschillende lesies. Bij individuele patienten kunnen er redenen zijn de ene lesie met ablatie te behandelen en een andere met TACE. Hierover wordt binnen deze module geen uitspraak gedaan.

Concluderend laten de acht geïncludeerde studies aanwijzingen zien voor een mogelijk positief effect van de combinatiebehandeling van TACE en ablatie op totale overleving, ziektevrijeoverleving en lokale tumorcontrole bij patiënten met tumoren van 3 tot 5 cm. Er werden klinisch relevante verschillen gevonden voor meerdere uitkomstmaten, maar de totale bewijskracht is onvoldoende om hier een eenduidige conclusie uit te trekken.

<u>Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)</u>

De combinatietherapie met TACE en ablatie resulteert in een grotere belasting voor de patiënt ten opzichte van een van beide behandelingen alleen. In de meeste studies wordt er een interval van 2 tot 4 weken tussen TACE en ablatie aangehouden. Voor patiënten betekent dit een extra opname en langer behandeltraject. Bovendien vergroot de extra

behandeling mogelijk de kans op complicaties. De geïncludeerde studies vonden evenwel geen significant hoger percentage complicaties bij de combinatie TACE en ablatie ten opzichte van ablatie alleen, maar de kwaliteit van het bewijs hiervoor werd als zeer onzeker beoordeeld. In individuele patienten (zie overwegingen hierboven) kunnen de extra belasting en risico's mogelijk opwegen tegen de potentieel hogere effectiviteit van de combinatiebehandeling.

Kosten (middelenbeslag)

De kosten van combinatiebehandeling en de benodigde inzet van medisch personeel en faciliteiten zijn hoger in geval van de combinatietherapie ten opzichte van monotherapie. Er is in het kader van deze richtlijn geen kostenanalyse verricht. De geïncludeerde studies wijzen op een betere ziektevrije overleving en lager lokaal recidief percentage. Het ligt in de rede dat dat leidt tot een afname van het aantal reinterventies wat kan compenseren voor de initieel hogere kosten van de combinatiebehandeling. Het beschikbare wetenschappelijk bewijs werd echter als laag tot zeer laag beschouwd en er kan derhalve geen eenduidige conclusie worden getrokken. Over kosteneffectiviteit van de combinatiebehandeling kan geen uitspraak worden gedaan.

Aanvaardbaarheid, haalbaarheid en implementatie

De werkgroep is van mening dat er geen bezwaren of voorwaarden zijn voor aanvaardbaarheid, haalbaarheid of implementatie van de aanbeveling.

Aanbevelingen

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

Er zijn verschillende gerandomiseerde studies die aantonen dat de combinatie TACE plus ablatie superieur is ten opzichte van ablatie alleen bij patiënten met een HCC groter dan 3 cm. We berekenden op basis van de geïncludeerde studies een relatief risico van respectievelijk 0.33 (95% CI: 0.16 to 0.66) en 0.65 (0.52 to 0.82) voor totale overleving na 1 en 3 jaar, ten gunste van de combinatiebehandeling. Dit heeft evenwel niet geleid tot een harde aanbeveling de combinatietherapie standaard aan te bieden in de klinische praktijk. Volgens de GRADE systematiek is de bewijskracht van onderliggende studies laag. De beschikbare studies kennen methodologische beperkingen en zijn niet gevalideerd in westerse populaties. Bovendien zijn de meeste studies gedateerd; sinds het verschijnen van deze studies zijn de ablatietechnieken en resultaten verbeterd (Cassinotto, 2021; Laimer, 2020; Puijk, 2022; Schullian, 2022). Daar staat niet alleen tegenover dat de verschillende studies wijzen op een gunstig effect, maar ook dat de rationale voor neoadjuvante TACE sterk is. Ten eerste leidt TACE tot krimp van een lesie, waardoor het makkelijker wordt een lesie compleet te ableren met voldoende marge. Ten tweede is als gevolg van de afsluiting van tumor-voedende arterieën, er een kleinere kans op een recidief als gevolg van 'heat-sink'. Ten derde vormt TACE een behandeling voor eventuele satelliet-metastasen, die nabij maar net buiten de ablatiezone zijn gelegen. Satelliet-metastasen komen zeer frequent voor bij HCC, met name bij grotere lesies, en liggen meestal in nabijheid van de primaire tumor. Voornoemde overwegingen hebben ertoe geleid dat twijfel persisteert over de toegevoegde waarde van neoadjuvante TACE bij patiënten met een HCC van 3-5 cm waarbij een ablatie is gekozen als behandeling van keuze. Er lijkt voldoende grond om dit aan te bevelen voor patiënten waarbij er twijfel bestaat of voldoende marge kan worden behaald. Met de TACE wordt dan beoogd de lesie te laten krimpen om zo een ablatie met voldoende marge te vergemakkelijken.

Overweeg TACE voorafgaand aan ablatie (tijdsinterval 4 tot 6 weken) bij patiënten met een irresectabel solitair HCC van 3-5 cm waarbij een ablatie wordt overwogen waar er twijfel is of er adequate ablatiemarges kunnen worden bereikt.

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Bijlagen bij module 7.2

Kennislacunes

Er is behoefte aan een goed uitgevoerde gerandomiseerde studie in een westerse populatie die een vergelijk maakt tussen TACE plus ablatie versus ablatie alleen in patiënten met een HCC 3-5 cm.

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
1e							
2e							
etc							

[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, et cetera.

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

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

Evidence tables

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

Research question: What is the effectiveness of the combination of transarterial chemoembolization (TACE) and ablation compared to TACE or ablation alone in patients with early stage HCC (BCLC A)?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Liu, 2011	Type of study: Open-label randomized controlled trial with blinded assessment. Setting: Chinese PLA General Hospital. Enrolled between May 2004 and December 2006. Country: China. Source of funding: No information. Conflicts of interest: Not clearly stated.	Patients with large unresectable hepatocellular carcinoma (>5cm); Inclusion criteria: • Presence of multiple lesions; • Tumor proximity to major vascular structures, which precluded the resection of a tumor-fee margin; • Or presence of severe cirrhosis with an insufficient hepatic functional reserve to tolerate conventional HCC resection Exclusion criteria: • No information. N total at baseline: N = 34 Intervention: N=16 Control: N=18	Intervention: TACE + percutaneous ablation with microwave ablation (MWA) 2–4 weeks after TACE	Control: TACE	Length of follow-up: Median follow-up of 8 months (range, 2–28 months) Loss-to-follow-up: No loss to follow-up Incomplete outcome data: No information.	**Overall survival** 1-year I: 33.3% C: 11.1% 2-year I: 6.25% C: 0% 3, 4, 5-years overall survival *not reported.* **Disease-free survival** *not reported.* **Local tumor control** *not reported.* **Complications** *Results are not stratified by treatment groups.*	Also reported: Follow-up imaging Definition: Tumor response was defined as a reduction in tumor size during the follow-up period Remarks: • Complications are reported, but not stratified by treatment groups. • Small number of participants • Conflicts of interests not clearly stated

		Important characteristics: Age, mean (SD): I: 52.1 y (14.5) C: 51.9 y (13.6) Sex, n/N (%) male: I: 14/16 (87.5%) C: 15/18 (83.3%) Size of the largest tumor (median, cm): I: 6.8 ± 1.5 C: 6.7 ± 1.5 Groups comparable at baseline? Yes.					
Liu, 2014	Type of study: Open-label randomized controlled trial. Setting: The First Affiliated Hospital of Bengbu Medical College. Enrolled between June 2005 and June 2011. Country: China. Source of funding: No information. Conflicts of interest: None to declare.	Patients with middle-late stage primary carcinoma of the liver who could or should not be accepted for surgical treatment, according with the AASLD diagnostic criteria Inclusion criteria: • Diagnosis of primary liver cancer • Nodular HCC, block type liver cancer, giant block type liver cancer, incorporation with a single carcinoma bolt in a non-main portal vein, combined with extrahepatic metastases , but through evaluation	Intervention: TACE followed by radiofrequency ablation (RFA)	Control: TACE	Length of follow-up: Not reported Loss-to-follow-up: No information. Incomplete outcome data: No information.	**Overall survival** 1,2, 3, 4, 5-years overall survival *not reported.* **Disease-free survival** *not reported.* **Local tumor control** *not reported.* **Complications** *Results are not stratified by treatment groups.* Eight patients (6.2%)	Also reported: Survival quality, liver function changes, tumor damage • Definition: Outcomes are not clearly defined Remarks: • Complications are reported, but not stratified by treatment groups • Quality of life was not clearly defined and not based on a QoL instrument • Small number of participants

		can be effectively controlled by RFA or radiation therapy <u>Exclusion criteria</u>: • No information. <u>N total at baseline</u>: N = 88 Intervention: N=45 Control: N=43 <u>Important characteristics</u>: Age, range: I: 45-75 C: 44-78 Sex, n/N (%) male: I: 36/45 (80.0%) C: 34/43 (79.1%) Tumor size (range, cm): I: 4-15 C: 5-14 Groups comparable at baseline? Yes.				developed liver function damage after all 125 RFA treatments.	• Conflicts of interests not clearly stated • Intervention not clearly defined (time period, etc).
Morimoto, 2010	<u>Type of study:</u> Open-label randomized controlled trial. <u>Setting:</u> Yokohama City University Medical Center.	Patients with solitary HCCs (diameter, 3.1-5.0 cm in the greatest dimension) <u>Inclusion criteria</u>: • ECOG performance ≤ 2; • Child-Pugh liver function class A or B	<u>Intervention:</u> Transcatheter arterial chemoembolization (TACE) was performed by selectively introducing a microcatheter into the right/left hepatic artery or tumor feeding arteries injecting epirubicin, lipiodol, and gelatin	<u>Control:</u> RFA	<u>Length of follow-up</u>: 3-year <u>Loss-to-follow-up</u>: No information.	**Overall survival** <u>1-year</u> I: 100% C: 89% <u>2-year</u> I: 93% C: 89%	Also reported: local tumor progression • Definition: The overall recurrence rate was measured from the date of randomization until the

	Enrolled between August 01, 2005 and April 2009. <u>Country:</u> Japan. <u>Source of funding:</u> Grant from Yokohama City University <u>Conflicts of interest</u>: No information.	• Lesion could be detected by ultrasonography; • TACE could be performed; • No evidence of portal and/or venous thrombosis, extrahepatic metastasis, or uncontrollable ascites; • Adequate haematological, hepatic and renal function. <u>Exclusion criteria</u>: • Patients who received any treatment for HCC • Patients who meet the criteria for surgical resection <u>N total at baseline</u>: N = 37 Intervention: N=19 Control: N=18 <u>Important characteristics</u>: Age, mean (range): I: 70 y (57-78) C: 73 y (48-84) Sex, n/N (%) male: I: 15/19 (79%) C: 12/18 (67%) Tumor diameter (mean, cm): I: 3.6 ± 0.7 C: 3.7 ± 0.6	sponge. Within 24 hours after TACE, radiofrequency ablation (RFA) was performed percutaneously using multitined expandable electrodes or internally cooled electrodes.		<u>Incomplete outcome data</u>: No information.	<u>3-year</u> I: 93% C: 80% Log-rank test, P=0.369 4, 5-years overall survival *not reported.* **Disease-free survival** *not reported.* **Local tumor progression rate** I: 6% C: 39% **Complications** Grade 1 to 2 I: 1/18 (5.6%) C: 5/19 (26.3%) *No grade ≥ 3 are reported*	date of detection of local tumor progression or new HCC foci in the liver in the arterial-phase CT images Remarks: • Small number of participants • Conflicts of interests not clearly stated

		Groups comparable at baseline? Yes.					
Peng, 2012	Type of study: Open-label randomized controlled trial. Setting: Cancer Center at Sun Yat-sen University Enrolled between January 2002 and December 2006. Country: China. Source of funding: Supported by the Sciences and Technology Committee of Guangdong Province, China (grant 2006B36002008), and the State Key Project on Infectious Diseases of China (grant 2012ZX10002-016) Conflicts of interest: None to declare.	Patients with recurrent HCC measuring 5 cm in diameter or smaller Inclusion criteria: • Age 18-75 years and refusal to undergo liver transplantation; • Recurrent HCC after curative treatment with RF ablation or hepatectomy; • No previous treatment for HCC; • No radiologic evidence of invasion into major portal and/or hepatic vein branches; • No extrahepatic metastases; • Lesions visible at ultrasonography (US), • With an acceptable and safe path between the lesion and the skin seen at US • No severe liver dysfunction or no significant coagulopathy; • No history of encephalopathy, ascites refractory to diuretics, or variceal bleedings; and	Intervention: TACE followed by RFA	Control: TACE	Length of follow-up: I: 39.2 months (21.1) C: 33.6 months (24.7) *Not stated by the authors if they report mean or median* Loss-to-follow-up: No information. Incomplete outcome data: No information.	**Overall survival** 1-year I: 94% C: 82% 3-year I: 69% C: 47% 5-year I: 46% C: 36% P=0.037(1 versus. 3 versus. 5-year) 2, 4-years overall survival *not reported.* **Disease-free survival** 1-year I: 80% C: 64% 3-year I: 45% C: 18% 5-year I: 40% C: 18%	Also reported: local tumor progression • Definition: Local tumor progression was defined as the appearance of tumor enhancement around the ablated area after treatment Remarks: • Small number of participants • CT unit was changed in during the study, which may have added some uncertainty to the results • Study was not registered • Source of funding unknown

		• Eastern Co-operative Oncology Group performance status of 0 Exclusion criteria: • No information N total at baseline: N = 139 Intervention: N=69 Control: N=70 Important characteristics: Age, mean (SD): I: 57.5 y (10.0) C: 55.1 y (9.5) Sex, n/N (%) male: I: 59/69 (85.6%) C: 55/70 (78.6%) Tumor size (mean, cm): I: 2.1 ± 0.5 C: 2.1 ± 0.4 Groups comparable at baseline? Yes.				P=0.005 (1 versus. 3 versus. 5-year) *2, 4-years disease-free survival not reported.* **Local tumor control** *not reported.* **Complications** Grade 3 I: 2/69 (2.9%) C: 2/70 (2.8%)	
Peng, 2013	Type of study: Open-label randomized controlled trial. Setting: Cancer Center at Sun Yat-sen University	Patients with recurrent HCC measuring ≤ 7 cm Inclusion criteria: • Age 18-75 years; • A solitary HCC ≤ 7 cm in diameter, or multiple HCC	Intervention: TACE followed by RFA	Control: RFA	Length of follow-up: Median (range) I: 47.5 months (29-62)	**Overall survival** 1-year I: 92.6% C: 85.3% 3-year I: 66.6% C: 59%	Remarks: • Small number of participants • The study was funded by one of the authors

	Enrolled between October 2006 and June 2009. <u>Country:</u> China. <u>Source of funding:</u> Supported by a grant from the National Natural Science Foundation of China (Grant No. 30872995), the State Key Project on Infectious Diseases of China (Grant No. 2012ZX10002-016), and the 5010 Foundation of Sun Yat-sen University (Grant No. 2007043 <u>Conflicts of interest</u>: None to declare.	lesions, each ≤ 3 cm in diameter • No radiologic evidence of invasion into major portal/hepatic venous branches and no extrahepatic metastases; • Lesions visible on ultrasound with an acceptable safe path between the lesion and skin; • An Eastern Cooperative Oncology Group performance status of 0; • No previous treatment; • Child-Pugh class A or B cirrhosis <u>Exclusion criteria</u>: • Severe coagulation disorders; • Evidence of hepatic decompensation; • Contraindications to carboplatin, epirubicin, mitomycin, or lipiodol. <u>N total at baseline</u>: N = 189 Intervention: N=94 Control: N=95 <u>Important characteristics</u>: Age, mean (SD): I: 53.3 y (11.0)			C: 47.0 months (28-62) <u>Loss-to-follow-up</u>: I: 1/84 (1.1%) C: 0 <u>Incomplete outcome data</u>: I: 1/84 (1.1%) Reason: withdrew C: 1/95 (1.1%) Reason: withdrew	<u>4-year</u> I: 61.8% C: 45% 2, 5-years overall survival *not reported.* **Disease-free survival** <u>1-year</u> I: 79.4% C: 66.7% <u>3-year</u> I: 60.6% C: 44.2% <u>4-year</u> I: 54.8% C: 38.9% *2, 5-years disease-free survival not reported.* **Local tumor control** *not reported.* **Complications** Grade 3 I: 2/94 (2.1%) C: 2/95 (2.1%)	

		C: 55.3 y (13.3) Sex, n/N (%) male: I: 75/94 (79.8%) C: 71/95 (74.7%) Size of main tumor (mean, cm): I: 3.47 ± 1.44 C: 3.39 ± 1.35 Groups comparable at baseline? Yes.					
Sheta, 2016	Type of study: Open-label randomized controlled trial. Setting: Algeish St Tanta University Hospital Unknown enrolment dates Country: Egypt. Source of funding: No information. Conflicts of interest: None to declare. .	Patients with non-resectable single-lesion HCC Inclusion criteria: • Child classification A or B; • Serum albumin≥3 g/l, serum bilirubin <2.5 mg/dl, platelet count≥70 000 mm^3, international normalized ratio ≤1.6, serum creatine <2mg/dl; • Tumor size more than 4 cm and confined to one lobe or the liver Exclusion criteria: • Portal vein thrombosis; • A technically inaccessible hepatic artery; • Metastatic HCC • More than one lesion; • Lesions in close proximity to the portal vein;	Intervention: Group B Single session: RFA followed by TACE Group C Single session: MWA followed by TACE	Control: Group A TACE	Length of follow-up: Not reported Loss-to-follow-up: No information. Incomplete outcome data: No information.	**Overall survival** *not reported.* **Disease-free survival** *not reported.* **Local tumor control** *not reported.* **Complications** I: 10% (group B) I: 10% (group C) C: 40% (group A)	Remarks: • Unknown baseline characteristics for age and sex • Small number of participants • Study was not registered • Source of funding unknown

		• Inferior vena cava or gall bladder; • Patients without extensive arteriovenous shunting <u>N total at baseline</u>: N = 50 Intervention: Group B TACE + RFA: N=20 Group C TACE + MWA: M=10 Control: Group A TACE: N=20 <u>Important characteristics</u>: Age: Not reported Sex, n/N (%) male: Not reported Size of lesion (mean, cm): I: 4.87 ± 0.42 (group B) I: 5.15 ± 0.27 (group C) C: 4.82 ± 0.57 (group A) Groups comparable at baseline? Unknown Authors stated: *In our three groups of patients with HCC, there was no statistically*					

		significant difference before intervention in age, sex, liver function tests, platelet count, Child class, size of the lesion, or position of the lesion as shown in (Table 1). The information regarding age and sex is not provided by the authors.					
Zaitoun, 2021	Type of study: Open-label randomized controlled trial. Setting: Zagazig University hospital Enrolled between January 2017 and May 2020. Country: Egypt. Source of funding: No information. Conflicts of interest: None to declare. .	Patients with HCC >3 - <5 cm Inclusion criteria: • Absence of extra-hepatic metastases; • Absence of a history of encephalopathy or refractory ascites; • Child classification A or B cirrhosis Exclusion criteria: • Poor patient compliance; • Severe coagulation disorder; • Portal vein thrombosis; • Renal impairment; • Previous local ablation therapy of HCC. N total at baseline: N = 278 Intervention: Combined (TACE+MWA) N=89	Intervention: TACE followed by MWA	Control: TACE Control: MWA	Length of follow-up: Not reported Loss-to-follow-up: No information. Incomplete outcome data: No information.	**Overall survival** 3-year I (combined): 62 (69.6%) C (TACE): 46 (54.8%) C (MWA): 50 (54.3%) P=-.02 **Disease-free survival** *not reported.* **Local tumor control** *not reported.* **Complications** I: 1.1% (TACE+MWA) C: 3.6% (TACE) C: 2.2% (MWA)	Remarks: • Unknown in which group the lost-to follow up occurred • Source of funding unknown

		Control: TACE: N=84 Control: MWA: N=92 <u>Important characteristics</u>: Age, mean (SD): I (Combined): 52.1 y (9.5) C (TACE): 51.3 y (9.2) C (MWA): 53.8 y (10.3) Sex, n/N (%) male: I (Combined): 52/89 (58.6%) C (TACE): 52/84 (61.9%) C (MWA): 50/92 (54.3%) Tumor size (mean, cm): I (Combined): 3.7 ± 0.8 C (TACE): 3.6 ± 0.8 C (MWA): 3.9 ± 0.9 Groups comparable at baseline? Yes.					
Zhang, 2021	<u>Type of study:</u> Open-label randomized controlled trial. <u>Setting:</u> Cancer Center at Sun Yat-sen University	Patients with recurrent HCC measuring ≤ 7 cm <u>Inclusion criteria</u>: • Age 18-75 years; • A solitary HCC ≤ 7 cm in diameter, or multiple HCC lesions, each ≤ 3 cm in diameter	<u>Intervention:</u> TACE followed by RFA	<u>Control:</u> RFA	<u>Length of follow-up</u>: 6 years after trial was closed <u>Loss-to-follow-up</u>: I: 3/94 (3.2%)	**Overall survival** <u>1-year</u> I: 94.9% C: 85.4% <u>3-year</u> I: 69.1% C: 57.9%	Remarks: • Follow-up study from Peng 2013. Results on overall survival and disease-free survival do not correspond. • Small number of participants

	(follow-up study from Peng 2013) Enrolled between October 2006 and June 2009. <u>Country:</u> China. <u>Source of funding:</u> supported by the National Natural Science Foundation of China (No. 81770608, 82072029) and the National High Level Talents Special Support Plan-Ten Thousand Plan-Young Top-notch Talent Support Program (Dr Peng). <u>Conflicts of interest</u>: None to declare.	• No radiologic evidence of invasion into major portal/hepatic venous branches and no extrahepatic metastases; • Lesions visible on ultrasound with an acceptable safe path between the lesion and skin; • An Eastern Cooperative Oncology Group performance status of 0; • No previous treatment; • Child-Pugh class A or B cirrhosis <u>Exclusion criteria</u>: • Severe coagulation disorders; • Evidence of hepatic decompensation; • Contraindications to carboplatin, epirubicin, mitomycin, or lipiodol. <u>N total at baseline</u>: N = 189 Intervention: N=94 Control: N=95 <u>Important characteristics</u>: Age, mean (SD): I: 53.3 y (11.0) C: 55.3 y (13.3) Sex, n/N (%) male:			C: 3/95 (3.2%) <u>Incomplete outcome data</u>: No information.	<u>5-year</u> I: 52.0% C: 43.2% <u>7-year</u> I: 36.4% C: 19.4% HR: 0.55 (95% CI, 0.39 to 0.78; p=0.001) **Disease-free survival** <u>1-year</u> I: 78.7% C: 64.2% <u>3-year</u> I: 54.3% C: 37.9% <u>5-year</u> I: 41.4% C: 27.4% <u>7-year</u> I: 34.5% C: 18.1% HR: 0.66 (95% CI, 0.49 to 0.89; p=0.007) **Local tumor control** *not reported.*	

		I: 75/94 (79.8%) C: 71/95 (74.7%) Size of main tumor (mean, cm): I: 3.47 ± 1.44 C: 3.39 ± 1.35 Groups comparable at baseline? Yes.				**Complications** Grade 3 I: 6/94 (6.4%) C: 2/95 (2.1%) *(results from Peng, 2013)*	

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 effectiveness of the combination of transarterial chemoembolization (TACE) and ablation compared to TACE or ablation alone in patients with early stage HCC (BCLC A)?

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

			Were data analysts blinded?				
	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**
Liu, 2011	Probably yes; Reason: Patients were consecutively enrolled at clinical presentation and were alternately assigned to one of the treatment groups.	Definitely no; Reason: Method was based on an open random allocation schedule.	Probably no; Reason: Open-label trial (patients and health care providers not blinded), outcome assessors blinded (blinding of data collectors and analysts not reported).	Definitely yes; Reason: No loss to follow-up.	Probably no; Reason: Results with regard to the complications are not stratified by treatment groups.	Definitely no; Reason: Open-label trial; CONSORT flow chart was not provided by the authors; incorrect numbers are presented in the article with regard to the tumor response; unclear if and to what constitutes the possible conflict of interest.	**HIGH**
Liu, 2014	Probably no; Reason: No information.	Probably no; Reason: No information.	Probably no; Reason: Open-label trial, no information provided by the authors.	Probably yes; Reason: No information.	Probably no; Reason: QoL was mentioned in the methods section, but the results only report the survival quality of the patients. Results with regard to the complications are not stratified by treatment groups.	Definitely no; Reason: Open-label trial; CONSORT flow chart was not provided by the authors; outcomes lack of a clear definition.	**HIGH**
Morimoto, 2010	Probably yes; Reason: Patients were consecutively enrolled at clinical presentation	Probably yes; Reason: Central registration.	Probably no; Reason: Open-label trial, no information	Probably yes; Reason: No information.	Probably yes; Reason: All outcome measures described in the trial protocol	Probably no; Reason: Open-label trial; CONSORT flow chart was not provided by the authors;	**Some concerns**

	and were alternately assigned to one of the treatment groups.		provided by the authors.		are reported in the results.	conflicts of interests not clearly stated.	
Peng, 2012	Definitely yes; Reason: Randomization was centralized and performed with a computer-generated allocation list.	Definitely yes: Reason: Allocation was put into sequentially numbered, opaque, sealed envelopes.	Probably no; Reason: Open-label trial (patients and health care providers not blinded), unknown if outcome assessors blinded were blinded.	Probably yes; Reason: No information.	Probably yes; Reason: The study assessed the outcome measures described in the clinical trial register.	Probably no; Reason: Open-label trial; CONSORT flow chart was not provided by the authors; unknown source of funding.	**Some concerns**
Peng, 2013	Definitely yes; Reason: Randomization was centralized and performed with a computer-generated allocation list.	Probably yes; Reason: Central allocation.	Probably yes; Reason: Open-label trial (patients and health care providers not blinded), outcome assessors blinded (blinding radiologist and statistician).	Probably yes Reason: Infrequent number of patients excluded from analysis due to withdrawn consent.	Probably yes; Reason: All outcome measures described in the trial protocol are reported in the results.	Probably no; Reason: Unknown source of funding (financial support by one of the authors).	**LOW**
Sheta, 2016	Probably no; Reason: No information.	Probably no; Reason: No information.	Probably no; Reason: Open-label trial, no information provided by the authors.	Probably yes; Reason: No information.	Probably yes; Reason: The study assessed the outcome measure described in the clinical trial register.	Probably no; Reason: Open-label trial; CONSORT flow chart was not provided by the authors; unknown source of funding; important baseline characteristics are not reported by the authors.	**HIGH**
Zaitoun, 2021	Probably yes; Reason: Patients were randomized to one of the three groups by one of the authors	Probably no; Reason: No information.	Probably no; Reason: Open-label trial, no information provided by the authors.	Probably no; Reason: Unknown in which group the	Probably yes; Reason: All outcome measures described in the trial protocol are reported in the results.	Probably no; Reason: Unknown source of funding.	**Some concerns**

	using serially numbered containers.			lost-to follow up (n=12) occurred.			
Zhang, 2021	Definitely yes; Reason: Randomization was centralized and performed with a computer-generated allocation list.	Probably yes; Reason: Central allocation.	Probably no; Reason: Open-label trial (patients and health care providers not blinded), unknown if outcome assessors blinded were blinded.	Probably yes; Reason: Infrequent number of patients excluded from analysis due to withdrawn consent.	Probably yes; Reason: All outcome measures described in the trial protocol are reported in the results.	Probably no; Reason: This is a follow-up study on Peng, 2013. The overall survival and disease-free survival results do not correspond.	**LOW**

Table of excluded studies

Reference	Reason for exclusion
Cao JH, Zhou J, Zhang XL, Ding X, Long QY. Meta-analysis on radiofrequency ablation in combination with transarterial chemoembolization for the treatment of hepatocellular carcinoma. J Huazhong Univ Sci Technolog Med Sci. 2014 Oct;34(5):692-700. doi: 10.1007/s11596-014-1338-5. Epub 2014 Oct 16. PMID: 25318879.	Systematic review did not address ablation as comparison (only TACE).
Chen QW, Ying HF, Gao S, Shen YH, Meng ZQ, Chen H, Chen Z, Teng WJ. Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2016 Jun;40(3):309-314. doi: 10.1016/j.clinre.2015.07.008. Epub 2015 Oct 1. PMID: 26428660.	Systematic review did not address TACE as comparison (only ablation).
Chen, Z. G. and Huang, C. Y. and Lian, F. and Zhao, Y. N. and Wu, G. B. Percutaneous radiofrequency ablation combined with transarterial chemoembolization versus surgical resection in the treatment for early-stage hepatocellular carcinoma: a Meta-analysis	Full text in Chinese.
Dong W, Zhang T, Wang ZG, Liu H. Clinical outcome of small hepatocellular carcinoma after different treatments: a meta-analysis. World J Gastroenterol. 2014 Aug 7;20(29):10174-82. doi: 10.3748/wjg.v20.i29.10174. PMID: 25110446; PMCID: PMC4123348.	Wrong comparisons.
Gu L, Liu H, Fan L, Lv Y, Cui Z, Luo Y, Liu Y, Li G, Li C, Ma J. Treatment outcomes of transcatheter arterial chemoembolization combined with local ablative therapy versus monotherapy in hepatocellular carcinoma: a meta-analysis. J Cancer Res Clin Oncol. 2014 Feb;140(2):199-210. doi: 10.1007/s00432-013-1528-8. PMID: 24077865.	Wrong comparison (monotherapy is not always TACE or ablation).
Gui CH, Baey S, D'cruz RT, Shelat VG. Trans-arterial chemoembolization + radiofrequency ablation versus surgical resection in hepatocellular carcinoma - A meta-analysis. Eur J Surg Oncol. 2020 May;46(5):763-771. doi: 10.1016/j.ejso.2020.01.004. Epub 2020 Jan 7. PMID: 31937433.	Wrong comparison (TACE+ablation versus surgical resection).
Guo W, He X, Li Z, Li Y. Combination of Transarterial Chemoembolization (TACE) and Radiofrequency Ablation (RFA) versus. Surgical Resection (SR) on Survival Outcome of Early Hepatocellular Carcinoma: A Meta-Analysis. Hepatogastroenterology. 2015 May;62(139):710-4. PMID: 26897959.	Wrong comparison (TACE+ablation versus surgical resection).
Han, X., & Lv, W. (2013). Transcatheter arterial chemoembolization combined with radiofrequency ablation for the treatment of hepatocellular carcinoma: A meta-analysis of long-term efficacy. *Journal of Interventional Radiology*, *22*(5), 387-391.	Full text in Chinese.
Jiang C, Cheng G, Liao M, Huang J. Individual or combined transcatheter arterial chemoembolization and radiofrequency ablation for hepatocellular carcinoma: a time-to-event meta-analysis. World J Surg Oncol. 2021 Mar 19;19(1):81. doi: 10.1186/s12957-021-02188-4. PMID: 33741001; PMCID: PMC7980330.	The systematic review included observational studies.
Jiang FQ, Lu W, Yang C, Du P, Ma JP, Yang J, Xie P, Zhang Z. Curative effect of transcatheter arterial chemoembolization combined with radiofrequency ablation in treating hepatic cell carcinoma and its effect on serum markers. Cancer Biomark. 2017 Jul 19;20(1):17-22. doi: 10.3233/CBM-160508. PMID: 28582848.	Included in selected systematic review (Li, 2021).
Jiang G, Xu X, Ren S, Wang L. Combining transarterial chemoembolization with radiofrequency ablation for hepatocellular carcinoma. Tumour Biol. 2014 Apr;35(4):3405-8. doi: 10.1007/s13277-013-1449-9. Epub 2013 Nov 26. PMID: 24277379.	The systematic review included observational studies.
Katsanos K, Kitrou P, Spiliopoulos S, Maroulis I, Petsas T, Karnabatidis D. Comparative effectiveness of different transarterial embolization therapies alone or in combination with local ablative or adjuvant systemic treatments for unresectable hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. PLoS One. 2017 Sep 21;12(9):e0184597. doi: 10.1371/journal.pone.0184597. PMID: 28934265; PMCID: PMC5608206.	Wrong comparisons.
Keshavarz P, Raman SS. Comparison of combined transarterial chemoembolization and ablations in patients with hepatocellular carcinoma: a systematic review and meta-analysis. Abdom Radiol (NY). 2022 Mar;47(3):1009-1023. doi: 10.1007/s00261-021-03368-2. Epub 2022 Jan 4. PMID: 34982183.	The systematic review included observational studies.
Kong QF, Jiao JB, Chen QQ, Li L, Wang DG, Lv B. Comparative effectiveness of radiofrequency ablation with or without transarterial chemoembolization for hepatocellular carcinoma. Tumour Biol. 2014 Mar;35(3):2655-9. doi: 10.1007/s13277-013-1349-z. Epub 2013 Nov 7. PMID: 24197985.	Systematic review did not address TACE as comparison (only ablation).

Lan T, Chang L, Mn R, Wu L, Yuan YF. Comparative Efficacy of Interventional Therapies for Early-stage Hepatocellular Carcinoma: A PRISMA-compliant Systematic Review and Network Meta-analysis. Medicine (Baltimore). 2016 Apr;95(15):e3185. doi: 10.1097/MD.0000000000003185. PMID: 27082558; PMCID: PMC4839802.	Wrong comparisons.
Li L, Tian J, Liu P, Wang X, Zhu Z. Transarterial chemoembolization combination therapy versus monotherapy in unresectable hepatocellular carcinoma: a meta-analysis. Tumori. 2016 Jun 2;2016(3):301-10. doi: 10.5301/tj.5000491. Epub 2016 Mar 22. PMID: 27002950.	Wrong comparisons.
Liao M, Huang J, Zhang T, Wu H. Transarterial chemoembolization in combination with local therapies for hepatocellular carcinoma: a meta-analysis. PLoS One. 2013 Jul 3;8(7):e68453. doi: 10.1371/journal.pone.0068453. PMID: 23844203; PMCID: PMC3701086.	The systematic review included observational studies.
Lin JJ, Wu W, Jiang XF, Jin XJ, Lu LJ, Bao LW. (Clinical outcomes of radiofrequency ablation combined with transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma: a single-center experience). Zhonghua Zhong Liu Za Zhi. 2013 Feb;35(2):144-7. Chinese. doi: 10.3760/cma.j.issn.0253-3766.2013.02.016. PMID: 23714672.	Full text in Chinese.
Liu B, Zhang Y, Chen H, Li W, Tsochatzis E. The combination of transcatheter arterial chemoembolisation (TACE) and thermal ablation versus TACE alone for hepatocellular carcinoma. Cochrane Database Syst Rev. 2022 Jan 4;1(1):CD013345. doi: 10.1002/14651858.CD013345.pub2. PMID: 34981511; PMCID: PMC8724539.	Systematic review did not address ablation as comparison (only TACE).
Liu C, Li T, He JT, Shao H. TACE combined with microwave ablation therapy versus. TACE alone for treatment of early- and intermediate-stage hepatocellular carcinomas larger than 5 cm: a meta-analysis. Diagn Interv Radiol. 2020 Nov;26(6):575-583. doi: 10.5152/dir.2020.19615. PMID: 32965220; PMCID: PMC7664747.	Systematic review did not address ablation as comparison (only TACE).
Liu H, Wang ZG, Fu SY, Li AJ, Pan ZY, Zhou WP, Lau WY, Wu MC. Randomized clinical trial of chemoembolization plus radiofrequency ablation versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. Br J Surg. 2016 Mar;103(4):348-56. doi: 10.1002/bjs.10061. Epub 2016 Jan 18. PMID: 26780107.	Wrong comparison (TACE+ablation versus surgical resection).
Liu, T. Z. and Shao, Y. W. and Yuan, G. P. Therapeutic effect of multipolar percutaneous radio-frequency ablation combined with TACE on massive hepatocellular carcinoma	Full text in Chinese.
Liu, Y., Zhuo, L., Zhu, B., HE, M., XU, Y., Wang, T., ... & Liu, G. (2017). Transcatheter arterial chemoembolization in combination with percutaneous ablation therapy for the treatment of hepatocellular carcinoma: a meta-analysis. *Journal of Interventional Radiology*, 830-835.	Full text in Chinese.
Liu Z, Gao F, Yang G, Singh S, Lu M, Zhang T, Zhong Z, Zhang F, Tang R. Combination of radiofrequency ablation with transarterial chemoembolization for hepatocellular carcinoma: an up-to-date meta-analysis. Tumour Biol. 2014 Aug;35(8):7407-13. doi: 10.1007/s13277-014-1976-z. Epub 2014 Apr 29. PMID: 24777334.	Systematic review did not address TACE as comparison (only ablation).
Lu Z, Wen F, Guo Q, Liang H, Mao X, Sun H. Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: a meta-analysis of randomized-controlled trials. Eur J Gastroenterol Hepatol. 2013 Feb;25(2):187-94. doi: 10.1097/MEG.0b013e32835a0a07. PMID: 23134976.	Systematic review did not address TACE as comparison (only ablation).
Majumdar A, Roccarina D, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Management of people with early- or very early-stage hepatocellular carcinoma: an attempted network meta-analysis. Cochrane Database Syst Rev. 2017 Mar 28;3(3):CD011650. doi: 10.1002/14651858.CD011650.pub2. PMID: 28351116; PMCID: PMC6464490.	Wrong comparison (surgery versus ablation).
Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer. 2010 Dec 1;116(23):5452-60. doi: 10.1002/cncr.25314. Epub 2010 Jul 29. PMID: 20672352.	Included in selected systematic review (Li, 2021).
Ni JY, Liu SS, Xu LF, Sun HL, Chen YT. Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma. World J Gastroenterol. 2013 Jun 28;19(24):3872-82. doi: 10.3748/wjg.v19.i24.3872. PMID: 23840128; PMCID: PMC3699038.	Systematic review did not address TACE as comparison (only ablation).
Ni, J. Y. and Liu, S. S. and Xu, L. F. and Sun, H. L. and Chen, Y. T. Meta-analysis of the combination of transarterial chemoembolization and radiofrequencyablation for treatment of hepatocellular carcinoma	Full text in Chinese.

Ni JY, Liu SS, Xu LF, Sun HL, Chen YT. Transarterial chemoembolization combined with percutaneous radiofrequency ablation versus TACE and PRFA monotherapy in the treatment for hepatocellular carcinoma: a meta-analysis. J Cancer Res Clin Oncol. 2013 Apr;139(4):653-9. doi: 10.1007/s00432-012-1369-x. Epub 2013 Jan 5. PMID: 23292073.	Overlap with selected systematic review (Li, 2021).
Ni, J. Y. and Sun, H. L. and Luo, J. H. and Wang, W. D. and Chen, Y. T. and Xu, L. F. Meta-analysis of randomized controlled trials: percutaneous radiofrequency ablation in the treatment of hepatocullular carcinoma	Full text in Chinese.
Peng ZW, Zhang YJ, Chen MS, Xu L, Liang HH, Lin XJ, Guo RP, Zhang YQ, Lau WY. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol. 2013 Feb 1;31(4):426-32. doi: 10.1200/JCO.2012.42.9936. Epub 2012 Dec 26. PMID: 23269991.	Included in selected systematic review (Li, 2021).
Peng ZW, Zhang YJ, Liang HH, Lin XJ, Guo RP, Chen MS. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. Radiology. 2012 Feb;262(2):689-700. doi: 10.1148/radiol.11110637. Epub 2011 Dec 12. PMID: 22157201.	Included in selected systematic review (Li, 2021).
Qu, X. Y. and Qin, C. H. and Wu, J. and Chen, Z. L. and Yang, W. J. Transcatheter hepatic arterial chemoembolization in combination with radiofrequency ablation for treatment of patients with hepatocellular carcinoma: Curative efficacy and effect on serum BDNF level	Full text in Chinese.
Sheta E, El-Kalla F, El-Gharib M, Kobtan A, Elhendawy M, Abd-Elsalam S, Mansour L, Amer I. Comparison of single-session transarterial chemoembolization combined with microwave ablation or radiofrequency ablation in the treatment of hepatocellular carcinoma: a randomized-controlled study. Eur J Gastroenterol Hepatol. 2016 Oct;28(10):1198-203. doi: 10.1097/MEG.0000000000000688. PMID: 27362551.	Included in selected systematic review (Li, 2021).
Tian G, Yang S, Yuan J, Threapleton D, Zhao Q, Chen F, Cao H, Jiang T, Li L. Comparative efficacy of treatment strategies for hepatocellular carcinoma: systematic review and network meta-analysis. BMJ Open. 2018 Oct 18;8(10):e021269. doi: 10.1136/bmjopen-2017-021269. PMID: 30341113; PMCID: PMC6196801.	Wrong comparisons.
Wang H, Liu Y, Shen K, Dong Y, Sun J, Shu Y, Wan X, Ren X, Wei X, Zhai B. A comparison between radiofrequency ablation combined with transarterial chemoembolization and surgical resection in hepatic carcinoma: A meta-analysis. J Cancer Res Ther. 2019;15(7):1617-1623. doi: 10.4103/jcrt.JCRT_503_19. PMID: 31939446.	Wrong comparison (TACE+ablation versus surgical resection).
Wang L, Ke Q, Lin N, Huang Q, Zeng Y, Liu J. The efficacy of transarterial chemoembolization combined with microwave ablation for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. Int J Hyperthermia. 2019;36(1):1288-1296. doi: 10.1080/02656736.2019.1692148. PMID: 31852267.	Systematic review did not address ablation as comparison (only TACE).
Wang W, Shi J, Xie WF. Transarterial chemoembolization in combination with percutaneous ablation therapy in unresectable hepatocellular carcinoma: a meta-analysis. Liver Int. 2010 May;30(5):741-9. doi: 10.1111/j.1478-3231.2010.02221.x. Epub 2010 Mar 18. PMID: 20331507.	There are more recent systematic reviews available.
Wang WD, Zhang LH, Ni JY, Jiang XY, Chen D, Chen YT, Sun HL, Luo JH, Xu LF. Radiofrequency Ablation Combined with Transcatheter Arterial Chemoembolization Therapy Versus Surgical Resection for Hepatocellular Carcinoma within the Milan Criteria: A Meta-Analysis. Korean J Radiol. 2018 Jul-Aug;19(4):613-622. doi: 10.3348/kjr.2018.19.4.613. Epub 2018 Jun 14. PMID: 29962868; PMCID: PMC6005934.	Wrong comparison (TACE+ablation versus surgical resection).
Wang X, Hu Y, Ren M, Lu X, Lu G, He S. Efficacy and Safety of Radiofrequency Ablation Combined with Transcatheter Arterial Chemoembolization for Hepatocellular Carcinomas Compared with Radiofrequency Ablation Alone: A Time-to-Event Meta-Analysis. Korean J Radiol. 2016 Jan-Feb;17(1):93-102. doi: 10.3348/kjr.2016.17.1.93. Epub 2016 Jan 6. PMID: 26798221; PMCID: PMC4720818.	Systematic review did not address TACE as comparison (only ablation).
Wang Y, Deng T, Zeng L, Chen W. Efficacy and safety of radiofrequency ablation and transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: A meta-analysis. Hepatol Res. 2016 Jan;46(1):58-71. doi: 10.1111/hepr.12568. Epub 2015 Sep 2. PMID: 26265000.	The systematic review included observational studies.

Xiong, L., Zhang, L., Ma, J., & Li, J. (2017). Efficacy of radiofrequency ablation plus hepatic arterial chemoembolization in primary hepatic carcinoma and its effect on serum markers. *International Journal Of Clinical And Experimental Medicine*, *10*(9), 14076-82.	Not included in selected systematic review (Li, 2021).
Yan S, Xu D, Sun B. Combination of radiofrequency ablation with transarterial chemoembolization for hepatocellular carcinoma: a meta-analysis. Dig Dis Sci. 2013 Jul;58(7):2107-13. doi: 10.1007/s10620-013-2570-8. Epub 2013 Jan 30. PMID: 23361576.	Systematic review did not address TACE as comparison (only ablation).
Yang DJ, Luo KL, Liu H, Cai B, Tao GQ, Su XF, Hou XJ, Ye F, Li XY, Tian ZQ. Meta-analysis of transcatheter arterial chemoembolization plus radiofrequency ablation versus transcatheter arterial chemoembolization alone for hepatocellular carcinoma. Oncotarget. 2017 Jan 10;8(2):2960-2970. doi: 10.18632/oncotarget.13813. PMID: 27936465; PMCID: PMC5356855.	Systematic review did not address ablation as comparison (only TACE).
Yi PS, Huang M, Zhang M, Xu L, Xu MQ. Comparison of Transarterial Chemoembolization Combined with Radiofrequency Ablation Therapy versus Surgical Resection for Early Hepatocellular Carcinoma. Am Surg. 2018 Feb 1;84(2):282-288. PMID: 29580359.	Wrong comparison (TACE+ablation versus surgical resection).
Yi Y, Zhang Y, Wei Q, Zhao L, Han J, Song Y, Ding Y, Lu G, Liu J, Ding H, Dai F, Tang X. Radiofrequency ablation or microwave ablation combined with transcatheter arterial chemoembolization in treatment of hepatocellular carcinoma by comparing with radiofrequency ablation alone. Chin J Cancer Res. 2014 Feb;26(1):112-8. doi: 10.3978/j.issn.1000-9604.2014.02.09. PMID: 24653633; PMCID: PMC3937757.	Included in selected systematic review (Li, 2021).
Yin, J., Lyu, T., Guan, H., Song, L., Wang, J., & Tong, X. (2017). Efficacy and safety of radiofrequency ablation combined with or without TACE for hepatocellular carcinomas: Meta-analysis. *Chinese Journal of Interventional Imaging and Therapy*, 606-612.	Full text in Chinese.
Yuan-Dong S, Hao Z, Hui-Rong X, Jing-Zhou L, Hui-Yong W, Jian-Jun H, Yu JM. Combination therapy: Meta-analysis of the effects of TACE and cryoablation on hepatocellular carcinoma. Medicine (Baltimore). 2019 Dec;98(49):e18030. doi: 10.1097/MD.0000000000018030. PMID: 31804309; PMCID: PMC6919413.	The systematic review included observational studies.
Zaitoun MMA, Elsayed SB, Zaitoun NA, Soliman RK, Elmokadem AH, Farag AA, Amer M, Hendi AM, Mahmoud NEM, Salah El Deen D, Alsowey AM, Shahin S, Basha MAA. Combined therapy with conventional trans-arterial chemoembolization (cTACE) and microwave ablation (MWA) for hepatocellular carcinoma >3-<5 cm. Int J Hyperthermia. 2021;38(1):248-256. doi: 10.1080/02656736.2021.1887941. PMID: 33615957.	Included in selected systematic review (Li, 2021).
Zhang, S. J., & Ma, Y. L. (2013). TACE combined with percutaneous microwave ablation in treatment of large primary hepatocellular carcinoma. *Chin J Interv Imaging Ther*, *10*(7), 397-400.	Full text in Chinese.
Zhao J, Wu J, He M, Cao M, Lei J, Luo H, Yi F, Ding J, Wei Y, Zhang W. Comparison of transcatheter arterial chemoembolization combined with radiofrequency ablation or microwave ablation for the treatment of unresectable hepatocellular carcinoma: a systemic review and meta-analysis. Int J Hyperthermia. 2020;37(1):624-633. doi: 10.1080/02656736.2020.1774667. PMID: 32525724.	Wrong comparison (TACE+MWA versus TACE+RFA).
Zhao J, Zhang H, Wei L, Xie S, Suo Z. Comparing the long-term efficacy of standard and combined minimally invasive procedures for unresectable HCC: a mixed treatment comparison. Oncotarget. 2017 Feb 28;8(9):15101-15113. doi: 10.18632/oncotarget.13145. PMID: 27835871; PMCID: PMC5362470.	Wrong comparisons.
Zhao, S. and Chen, X. C. and Long, Q. Y. and Zhang, X. L. Transcatheter arterial chemoembolization combined with radiofrequency ablation for the treatment of hepatocellular carcinoma: A systematic review and meta analysis	Full text in Chinese.
Zheng RN, You ZJ, Lin SH, Jia J, Cai YM, Liu C, Han S, Wang SM. Efficacy of percutaneous radiofrequency ablation for the treatment of hepatocellular carcinoma. Genet Mol Res. 2015 Dec 22;14(4):17982-94. doi: 10.4238/2015.December.22.24. PMID: 26782445.	Systematic review did not address TACE as comparison (only ablation).

Literature search strategy

Algemene informatie

Richtlijn: NVMDL hepatocellulair carcinoom	
Uitgangsvraag: Is de combinatie behandeling TACE (Transarterial Chemoembolization) en ablatie beter dan TACE of ablatie alleen beter bij patiënten met early stage HCC 3-5cm wat betreft overleving?	
Database(s): Ovid/Medline, Embase	Datum: 8-2-2022
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 elementen: Hepatocellulair carcinoom EN TACE EN ablatie Alle sleutelartikelen worden gevonden.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 3 februari 2022 met relevante zoektermen gezocht naar systematische reviews en RCTs over de combinatie behandeling TACE (Transarterial Chemoembolization) en ablatie. De literatuurzoekactie leverde 515 unieke treffers op.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	284	126	305
RCTs	189	124	210
Observationele studies			
Overig			
Totaal			515

5

Zoekstrategie

Embase

No.	Query	Results
#16	#5 AND #15	**5**
#15	#11 OR #12 OR #13 OR #14	**6**
#14	peng AND 2013 AND ablation AND radiofrequency AND randomized AND chemoemboliz ation NOT zhao	**2**
#13	radiofrequency AND ablation AND plus AND 'drug eluting' AND beads AND transcatheter AND arterial AND chemoembolization AND for AN D the AND treatment AND of AND single AND large AND hepatocellular AND carcinoma A ND iezzi	**2**
#12	efficacy AND safety AND of AND combined AND transcatheter AND arterial AND chemoe mbolization AND for AND hepatocellular AND carcinomas AND compared AND with AND radiofrequency AND ablation AND alone AND wang	**1**
#11	combined AND therapy AND with AND conventional AND 'trans arterial' AND chemoembolization AND zaitoun	**1**
#10	#9 NOT #8	**189**
#9	#5 AND #7 RCT	**287**
#8	#5 AND #6 SR	**284**

#7	'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	**1870795**
#6	'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	**796354**
#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)	**3182**
#4	#1 AND #2 AND #3	**5673**
#3	'ablation therapy'/exp OR ablati*:ti,ab,kw OR rfa:ti,ab,kw OR mwa:ti,ab,kw	**195450**
#2	'chemoembolization'/exp OR 'chemoemboli?ation*':ti,ab,kw OR tace:ti,ab,kw	**25321**
#1	'liver cell carcinoma'/exp OR ('liver cancer'/de AND 'primary tumor'/exp) OR ((hepat* NEAR/3 carcinom*):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw OR ((primary NEAR/2 liver):ti,ab,kw)	**231780**

Ovid/Medline

#	Searches	Results
11	10 not 9	124 RCT
10	7 and 8	188
9	6 and 8SR	126
8	5 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1504
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/)	1349237

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/))	545202
5	limit 4 to yr="2010 -Current"	1553
4	1 and 2 and 3	2046
3	exp Ablation Techniques/ or ablati*.ti,ab,kf. or rfa.ti,ab,kf. or mwa.ti,ab,kf.	199363
2	Chemoembolization, Therapeutic/ or chemoemboli?ation*.ti,ab,kf. or tace.ti,ab,kf.	12046
1	Carcinoma, Hepatocellular/ or ((hepat* or liver) adj3 carcinom*).ti,ab,kf. or hepatocarcinom*.ti,ab,kf. or hepatoma.ti,ab,kf. or (primary adj3 liver).ti,ab,kf.	155429

Module 8 Trans-arteriële radioembolisatie (TARE) versus systeemtherapie

Uitgangsvraag

Wat is de plaats van TARE ten opzichte van systeemtherapie bij de behandeling van patiënten met (lokaal) gevorderd HCC die niet in aanmerking komen voor chirurgie, ablatie of TACE?

Inleiding

TARE is een vorm van inwendige bestraling van de lever. TARE wordt toegepast indien in opzet curatieve behandelingen als chirurgie of ablatie niet meer haalbaar en/of zinvol zijn of als alternatief voor TACE. Aangezien TARE-behandeling uitsluitend de lever behandelt, is er voor patiënten met evidente extra-hepatische ziekte geen voordeel van TARE te verwachten. In deze module wordt specifiek gekeken naar de uitkomsten van TARE ten opzichte van systeemtherapie.

Search and select

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

What is the effectivity of treatment with TARE compared to treatment with systemic therapy in patients with without other local treatment options.

PICO

P: p*atients with a diagnosis of (locally) advanced hepatocellular carcinoma;*
I: SIRT/TARE;
C: systemic therapy;
O: overall survival, progression-free survival, response rate, adverse events, quality of life.

Relevant outcome measures

The guideline development group considered overall survival and progression-free survival as a crucial outcome measure for decision making; and response rate, complications/adverse events and quality of life as important outcome measures for decision making.

The guideline development group defined the outcome measures as follows:

Overall survival (OS)	Time from randomisation to death from any cause, with a minimum follow-up of 1 years
Progression-free survival (PFS)	Time from randomisation or initiation of treatment to the occurrence of disease progression or death, with a minimum follow-up of 1 year
Tumour response rate (TRR)	Response rate,
Adverse events (AE)	Grade ≥ 3
Quality of life (QoL)	Overall QoL, measured with a validated and reliable instrument

Clinically relevant difference

The guideline development group defined a minimal clinically relevant difference at a minimum of weeks) *(in line with the "NVMO-commissie ter Beoordeling van Oncologische Middelen (BOM)"criteria that were used until May 2023)* of:

- Overall survival: >12 weeks or HR <0.7.
- Progression-free survival: > 12 weeks or HR <0.7 .

And, in case of absence of a clinically relevant difference in overall survival or progression-free survival:

- Response rate: An absolute difference of 5%.
- Quality of life: A minimal clinically important difference of 10 points on the quality of life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Adverse events: Statistically significant less complications/adverse events.

Statistical methods

Statistical analyses were conducted using Review Manager (RevMan) software 5.4. For dichotomous outcomes, Mantel Haenszel random-effects risk ratios (RRs) and risk differences (RDs) were calculated. For continuous outcomes, a random-effects mean difference (MD) weighted by the inverse variance was calculated. The random-effects model estimates the mean of a distribution of effects. A meta-analysis was performed to pool the results if data was available for at least 3 of the included studies.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until April 15th, 2022. The detailed search strategy is depicted under the tab Methods.

The systematic literature search resulted in 312 hits. Studies were selected based on the following criteria:

- included patients HCC, ineligible for surgical intervention;
- compared systemic therapy;
- reported at least one of the outcomes of interest;
- the study design is a systematic review (SR) (preferably of randomized controlled trials; RCTs), or RCT;
- written in English language.

Based on title and abstract screening, 10 studies were initially selected. After reading the full text and thorough assessment of the studies, 6 studies were excluded (see table with reasons for exclusion under the tab Methods), and 4 study were included.

Results

In total, 4 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

Chow (2018) – SIRveNIB described a phase III, open-label randomized controlled trial, which was conducted in 11 countries (27 sites) in the Asia-Pacific region. They evaluated the efficacy and safety of Selective Internal Radiation Therapy (SIRT) in patients with unresectable hepatocellular carcinoma (HCC). Of 498 patients, 360 patients were included as they met the inclusion criteria and were willing to participate. These patients were randomized to receive SIRT (n=182) or sorafenib (n=178). The mean (SD) age was 59.5 (12.9) years in the intervention group, compared with 57.7 (10.6) years in the control group. In the intervention group 147/182 (80.8%) were males, compared with 151/178 (84.8%) in the control group. Patients who were randomly assigned to the SIRT group underwent angiographic and MAA assessment of suitability for SIRT. Eligible patients received a single delivery of SIRT with ^{90}Y-resin microspheres (2 to 5 weeks after randomization). Patients in

the intervention group received oral sorafenib (400 mg twice daily). The anticipated study duration was 5 years. The following relevant outcome measures were included: OS, PFS, TRR, AE, QoL.

Vilgrain (2017) – SARAH described a phase III, open-label randomized controlled trial, which was conducted at 25 sites in France. They evaluated the efficacy and safety of (SIRT) in patients with unresectable hepatocellular carcinoma (HCC). Of 496 patients, 467 patients were included as they met the inclusion criteria and were willing to participate. These patients were randomized to receive SIRT (n=237) or sorafenib (n=222). The median (IQR) age was 66 (60-72) years in the intervention group, compared with 65 (58-73) years in the control group. In the intervention group 212/237 (89%) were males, compared with 202/222 (91%) in the control group. Patients who were randomly assigned to the SIRT with ^{90}Y-resin microspheres underwent angiography, protective coiling and MAA-SPECT/computerised tomography scan and were readmitted for SIRT 1 or 2 weeks later. In bilobar tumours, the first treatment was delivered to the hemiliver with the greatest tumour burden and the contralateral hemiliver was scheduled for treatment 30–60 days after the first treatment. If the tumour progressed, SIRT could be repeated. Patients in the intervention group received oral sorafenib (400 mg twice daily). The anticipated study duration a minimum of 12 months. The following relevant outcome measures were included: OS, PFS, TRR, AE.

Pereira (2021) – SARAH is an ancillary study of the SARAH trial that compares the health-related quality of life (HRQoL) in patients who received either SIRT or at least one dose of sorafenib and who had at least one QoL follow-up assessment. Of the original 496 patients participating in the SARAH trial, 285 were included in this study. These patients were randomized to receive SIRT (n=122) or sorafenib (n=163). The following relevant outcome measure was included: QoL

Overall survival (OS) (crucial)
Two studies (Chow, 2018; Vilgrain, 2017) reported the median overall survival.

Chow (2018) reported OS, which was defined as the time from the date of random assignment to death as a result of any cause or the last follow-up date if the patient was alive. The median OS was 8.8 months in the intervention group, compared with 10.0 months in the control group. This resulted in a HR of 1.12 (95% CI 0.90 to 1.39).

Vilgrain (2017) reported OS, which was defined as the time from the date of random assignment to death as a result of any cause or the last follow-up date if the patient was alive. The median OS was 8.0 months in the intervention group, compared with 9.9 months in the control group. This resulted in a HR of 1.15 (95% CI 0.94 to 1.41).

<u>Level of evidence of the literature</u>
The level of evidence started as high, because the studies were RCTS. The level of evidence was downgraded by 2 levels, because of study limitations (risk of bias, -1 (see RoB assessment)) and low number of patients (imprecision, -1). . Therefore, level of evidence for the outcome 'o*verall survival'* is considered *low.*

Progression-free survival (PFS) (Crucial)
Two studies (Chow, 2018; Vilgrain, 2017) reported the progression free survival (PFS).

Chow (2018) reported the PFS. The median PFS was 5.8 months in the intervention group, compared with 5.1 months in the control group. This resulted in a HR of 0.89 (95% CI 0.7 to 1.1). This difference is not considered clinically relevant.

Vilgrain (2017) reported the PFS. The median PFS was 4.1 months in the intervention group, compared with 3.7 months. This resulted in a HR of 1.03 (95% CI 0.85 to 1.25). This difference is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTS. The level of evidence was downgraded by 2 levels, because of study limitations (risk of bias, -1 (see RoB assessment)) and low number of patients (imprecision, -1). Therefore, level of evidence for the outcome 'progression-free survival' is considered *low.*

Response rate (important)

Vilgrain (2017) reported the tumour response rate, defined as the proportion of patients with a best response of complete response or partial response according to RECIST version 1.1. In the intervention group, 36/190 (19%) evaluable patients achieved a complete response (n=5) or partial (n=31) response. In the control group 23/198 (12%) evaluable patients achieved a complete (n=2) or a partial response (n=21) (RR 1.63, 95% CI 1.01 to 2.65; RD 0.07, 95% CI 0.00 to 0.14)). This difference is considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTS. The level of evidence was downgraded by 3 levels, because of study limitations (risk of bias, -1 (see RoB assessment)) and data was originated from one study with a small number of included patients (serious imprecision, -2). Therefore, level of evidence for the outcome 'response rate' is considered *very low.*

Serious adverse events (AE) (important)

Two studies (Chow, 2018; Vilgrain, 2017) reported the serious adverse events, defines as grade ≥ 3.

Chow (2018) reported the serious adverse events defined as grade ≥ 3. In the intervention group, 36/130 (27.7%) patients experienced a serious events, compared with 82/162 (50.6%) in the control group (RR 0.82, 95% CI 0.59 to 1.15; RD -0.23, 95% CI -0.34 to -0.12).

Vilgrain (2017) reported the serious adverse events defined as grade ≥ 3. In the intervention group, 92/226 (40.7%) patients experienced a serious events, compared with 136/216 (63.0%) in the control group (RR 0.64, 95% CI 0.54 to 0.78; RD -0.19, 95% CI -0.28 to -0.10).

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTS. The level of evidence was downgraded by 2 levels, because of study limitations (risk of bias, -1 (see RoB assessment)) and low number of patients (imprecision, -1). . Therefore, level of evidence for the outcome '*serious adverse events*' is considered *low.*

Quality of Life (important)

Two studies reported the outcome Quality of life (Chow, 2028; Pereira, 2021).

Chow (2018) measured the QoL with the EQ5D, which is not a specific index for liver disease. Quantitative data was not reported. There were no statistically significant differences in the EQ-5D index between the TARE and sorafenib groups throughout the study in either the ITT or the per-protocol populations.

Pereira (2021) measured the QoL with the QLQ-C30 and the specific hepatocellular carcinoma module (QLQ-HCC18). At baseline, the global health score was 65.3 (n=110) in the intervention group, compared to 65.1 (n=154). The global health score at 12 months was 63.5 (n=21) in the intervention group, compared to 54.1 (n=22) in the control group.

Although there was a significant treatment effect ($p = 0.006$), and a significant time effect ($p < 0.0001$) on global health status, no treatment by time interaction was observed ($p = 0.12$). This difference is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTS. The level of evidence was downgraded by 3 levels, because of study limitations (risk of bias, -1 (see RoB assessment)) and low number of patients (imprecision, -1) and differences in outcome measures (indirectness, -1). Therefore, level of evidence for the outcome 'progression-free survival' is considered *very low.*

Conclusions

Overall survival (crucial)

Low GRADE	Treatment with TARE (resin microspheres using BSA-method) may result in little to no difference in **overall survival** when compared with treatment with systemic therapy in patients with unresectable hepatocellular carcinoma. *Sources: (Chow, 2018; Vilgrain, 2017)*

Progression-free survival (crucial)

Low GRADE	Treatment with TARE (resin microspheres using BSA-method) may result in little to no difference in **progression-free survival** when compared with treatment with systemic therapy in patients with unresectable hepatocellular carcinoma. *Sources: (Chow, 2018; Vilgrain, 2017)*

Tumour response rate (important)

Very low GRADE	The evidence is very uncertain about the effect of treatment on the **tumour response rate** with TARE (resin microspheres using BSA-method) when compared with treatment with systemic therapy in patients with unresectable hepatocellular carcinoma. *Sources: (Vilgrain, 2017)*

Serious adverse events (important)

Low GRADE	Treatment with TARE (resin microspheres using BSA-method) may result in little to no difference in **serious adverse events** when compared with treatment with systemic therapy in patients with unresectable hepatocellular carcinoma.

	Sources: (Chow, 2018; Vilgrain, 2017)

Quality of life (important)

Very low GRADE	The evidence is very uncertain about the effect of treatment on the **quality of life** with TARE (resin microspheres using BSA-method) when compared with treatment with systemic therapy in patients with unresectable hepatocellular carcinoma. *Sources: (Chow, 2018; Pereira, 2021)*

Overwegingen – van bewijs naar aanbeveling

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

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met TARE in vergelijk met sorafenib. Tot en met 15 april 2022 werden er 2 gerandomiseerde gecontroleerde studies (RCTs) gevonden; SARAH (Vilgrain, 2017; Pereira, 2021) en SIRveNIB (Chow, 2018).

Er werden alleen RCTs geïncludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. De geïncludeerde studies hadden in wisselende mate methodologische beperkingen (risk of bias). Er was in sommige studies een risico op bias door onder andere ontoereikende documentatie, lost of follow-up en missende data. Overigens is het in deze setting niet mogelijk enige risk of bias te vermijden, omdat de gerandomiseerde studies niet dubbel-blind worden uitgevoerd. Daarnaast waren er meerdere studies met een relatief kleine populatie en mede hierdoor een grote spreiding van de puntschatter van de uitkomstmaat (imprecision), waardoor de kwaliteit van dit bewijs ook naar beneden werd bijgesteld. De bewijskracht van de literatuur bij patiënten met een hepatocellulair carcinoom (HCC) werd voor zowel de cruciale als belangrijke uitkomstmaten, door bovenstaande bevindingen gegradeerd als ‘laag’ of ‘zeer laag’.

Concluderend zijn er nu twee relatief grote en redelijk kwalitatieve RCTs beschikbaar die het effect van TARE bij HCC onderzochten. Beide studies laten geen aanwijzingen zien voor een superieure effectiviteit van TARE boven sorafenib op de totale overleving en progressie vrije overleving. Wel was er sprake van een klinisch relevant verschil op tumorrespons bij TARE in vergelijking met Sorafenib.

Overige overwegingen

Patiënten met een hepatocellulair carcinoom waarbij geen lokale behandeloptie in de vorm van resectie, ablatie of TACE-behandeling mogelijk is, hebben op basis van de huidige literatuur geen duidelijk voordeel van TARE ten opzichte van systeemtherapie. Toch zijn er een aantal belangrijke kanttekeningen te maken ten aanzien van de toepasbaarheid van de geïncludeerde studies in het huidige behandellandschap.

Ten eerste is de gebruikte systeemtherapie in de studies (sorafenib) minder potent dan de huidige standaard combinatie behandeling van atezolizumab met bevacizumab. Ten tweede is in de huidig opgenomen onderzoeken technisch ondergeschikte dosimetrie van TARE toegepast. In de studies werd gebruik gemaakt van de zogenaamde body surface area (BSA) methode voor de berekening van de toe te dienen activiteit. Die methode houdt geen rekening met de daadwerkelijke dosis in de tumor en in het omringende leverweefsel, en leidt tot structurele onder-dosering. Inmiddels hebben studies aangetoond dat met geïndividualiseerde dosimetrie (i.e. therapeutische dosis in de tumor gecombineerd met

veilige dosis in het omringende leverweefsel) betere resultaten kunnen worden behaald (Garin, 2020). Dit werd ook aangetoond in een post hoc analyse van de SARAH studie (Hermann, 2020).

Door het ontbreken van gerandomiseerde studies met de huidige standaard systeemtherapie en beperkingen in de gebruikte dosimetrie van TARE is er geen advies te geven over prioritering van de behandeling TARE versus atezolizumab met bevacizumab. Wel was een van de inclusiecriteria van de IMbrave 150 studie dat er geen lokale behandelopties meer waren. Echter, in deze studie werd niet gepubliceerd waar deze lokale behandeling uit bestond en of dit ook TARE was. In een post-hoc analyse van de IMbrave 150 werd specifiek gekeken naar eerdere lokale behandeling (i.e., TACE of DEB-TACE) en grootte en aantal tumoren. Uit die studie bleek dat behandeling met atezolizumab en bevacizumab op alle fronten effectiever was dan sorafenib, onafhankelijk van aard en aantal voorbehandelingen of grootte en aantal tumoren (Salem, 2021). Dit werd verder bevestigd door een update van de IMbrave 150 studie een jaar na de primaire analyse (Cheng, 2022). Daarnaast dient in overweging te worden genomen of er bij de individuele patiënt voordeel van systeemtherapie of juist van TARE wordt verwacht. Hierbij worden o.a. het beloop van ziekte, onderliggend leverlijden en -functie, portale hypertensie, auto-immuun co-morbiditeit en cardiovasculaire status meegewogen. Studies spreken elkaar echter tegen over de associaties tussen onderliggend lijden en effectiviteit van immuuntherapie (Pfister, 2021; Espinoza, 2023; Ho, 2020). Daarom is het advies om elke patiënt in een expertcentrum in een multidisciplinair team te bespreken ten aanzien van de prioritering TARE versus atezolizumab plus bevacizumab.

Waarden en voorkeuren van patiënten (en eventuee hun verzorgers)

Voor de patiënten is met name van belang dat de beslissing in samenspraak met de patiënt, en met de juiste expertise aan tafel de behandeling wordt gekozen. Zie hiervoor ook de module 7.1 organisatie van zorg bij diagnostiek. Vanwege het wellicht mildere toxiciteitsprofiel van TARE versus systeemtherapie, moet hier ook gedacht worden aan de oudere patiënt, co-morbiditeit, en frequentie van ziekenhuisbezoek.

Kosten (middelenbeslag)

In verschillende studies werd kosteneffectiviteit bestudeerd. In een Italiaanse studie, waarbij data geanalyseerd werd van 389 patiënten die behandeld werden middels TARE en 241 patiënten die behandeld werden middels sorafenib, werd gevonden dat in intermediate BCLC-stadium B, behandeling middels TARE een 'incremental cost-utility ratio (ICUR)' heeft van 3.302 euro/QALY. Bij advanced BCLC-stadium C was TARE op alle fronten dominant (i.e., minder kosten, meer verbetering in gezondheid) (Rognoni, 2017). Deze bevindingen werden bevestigd in een meer recente kosteneffectiviteitsanalyse die gebruikmaakte van de data van de SARAH en de SIRveNIB studie. In deze analyse was de gevonden ICUR voor TARE in vergelijking met sorafenib 14.948 dollar/QALY, wat eveneens beschouwd kan worden als kosteneffectief (Agirrezabal, 2023).

Aanvaardbaarheid, haalbaarheid en implementatie

De werkgroep is van mening dat er geen bezwaren of voorwaarden zijn voor aanvaardbaarheid, haalbaarheid of implementatie van de aanbeveling.

Aanbeveling

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

Omdat er geen duidelijke voorkeur uit de literatuur komt voor TARE versus systeemtherapie, kan het beste multidisciplinair en samen met de patiënt beslist worden in welke situatie welke behandeling het beste past.

Tekst:
Beslis multidisciplinair of TARE danwel palliatieve systeemtherapie de voorkeur heeft in een centrum met expertise op het gebied van behandeling van HCC (refereer naar nieuwe SONCOS-richtlijnen van 2023) in het kader van patiënten met een (lokaal) gevorderd hepatocellulair carcinoom, waarbij geen resectie, ablatie of TACE mogelijk is. Ten aanzien van systeemtherapie, zie module 6 (referentie naar module 6).

Selectie van patiënten voor TARE en het uitvoeren van TARE zelf dient te gebeuren op basis van dosimetrie, i.e. een voldoende effectieve tumor dosis en veilige dosis op het omringende leverweefsel.

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Bijlagen bij module 8

Evidence table

5 **Evidence table for intervention studies**

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Chow, 2018 (SIRveNIB) NCT01135056	Type of study: RCT (open-label) Setting and country: a prospective, phase III, open label, multicentre, randomised controlled trial. The study was conducted at 27 sites in the Asia-Pacific region Funding and conflicts of interest: Financial support provided by Sirtex Medical Inc, Sydney, Australia. Conflicts of interest are disclosed	<u>Inclusion criteria</u>: • Aged ≤18 years with a locally advanced HCC (BCLC stage B or C without extrahepatic disease) with or without PVT • Not amenable to curative treatment modalities <u>Exclusion criteria</u>: • Received more than two previous administrations of hepatic artery-directed therapy • Hepatic artery-directed treatment within 4 weeks • Previous treatment with sorafenib or vascular endothelial growth factor inhibitors • Previous radiotherapy <u>N total at baseline</u>: Intervention: 182	SIRT (with yttrium-90 resin microspheres) SIRT started 2-5 weeks after randomisation Patients underwent angiographic and MAA assessment of suitability for SIRT. Eligible patients received a single delivery of SIRT	sorafenib Continuous oral sorafenib (400 mg twice daily)	<u>Length of follow-up</u>: 5 years <u>Loss-to-follow-up</u>: Intervention: N=12 (6.6%) Control: N=9 (5.1%) <u>Incomplete outcome data</u>: Intervention: N=52 (28.6%) Reasons: did not reive allocated intervention (n=52)* Liver-to-lung shunting exceeded 20% (n=24), unfavourable hepatic arterial anatomy (n=5), ineligible for the radioembolization for other reasons (n=8)	<u>Overall survival</u> (ITT cohort) Median OS (months) I: 8.8 C: 10.0 HR 1.12 (95% CI 0.9-1.14) p=0.36 <u>Progression-free survival</u> Median PFS (months) I: 5.8 C: 5.1 HR 0.89 (95% CI 0.7-1.1) P=0.31 <u>Tumour response rate</u> I: 16.5% (all partial response rate, 0% achieved a complete response) C:1.7% (all partial response rate,	• There were more patients in the SIRT group than in the sorafenib group who did not receive the assigned treatment • HRQoL was measured using the EQ-5D questionnaire, which is not a specific index for liver disease <u>Authors conclusion:</u> • "In patients with locally advanced HCC, OS did not differ significantly between RE and sorafenib. The improved toxicity profile of RE may inform treatment choice in selected patients."

		Control: 178 <u>Important prognostic factors</u>: Age, mean (SD): I: 59.5 (12.9) C: 57.7 (10.6) Sex: I: 80.8% M C: 84.8% M Groups comparable at baseline? Yes			patient withdrew consent (n=10), other (n=7) **by adding the numbers from the published article it seems that 2 participants are missing in the CONSORT diagram* Control: N=16 (9.0%) Reasons: did not reive allocated intervention (n=16), patient withdrew consent (n=12), other (n=4)	0% achieved a complete response) <u>Adverse events</u> Grade ≥ 3 I: 36/130 (27.7%) C: 82/162 (50.6%) *A detailed record of all adverse events is reported in the article.* <u>Quality of life</u> There were no statistically significant differences in the EQ-5D index between the SIRT and sorafenib groups throughout the study in either the ITT or the per-protocol populations	
Vilgrain, 2017 (SARAH) NCT01482442	Type of study: RCT (open-label) Setting and country: a prospective, phase III, open label, multicentre,	<u>Inclusion criteria</u>: • Aged ≤18 years with a life expectancy >3 months • ECOG performance status score of 0 or 1 • Child-Pugh liver function class A or B score of 7 or lower	SIRT (with yttrium-90 resin microspheres) Patients underwent angiography, protective coiling and MAA SPECT/computerised tomography scan and were readmitted for SIRT 1 or 2	sorafenib Continuous oral sorafenib (400 mg twice daily	<u>Length of follow-up</u>: Minimum of 12 months or until death <u>Loss-to-follow-up</u>: Intervention: N=11 (4.6%) Reasons: worsening disease (n=3), early	<u>Overall survival</u> (ITT cohort) Median OS (months) I: 8.0 (95% CI 6.7-9.9) C: 9.9 (95% CI 8.7-11.4)	• There were more patients in the SIRT group than in the sorafenib group who did not receive the assigned treatment. • The time between randomisation and treatment was much

	randomised controlled trial. The study was conducted at 25 sites in France Funding and conflicts of interest: Financial support provided by Assistance Publique—Hôpitaux de Paris and by Sirtex Medical Inc, Sydney, Australia. Conflicts of interest are disclosed	• Locally advanced HCC, or new HCC carcinoma not eligible for surgical resection, liver transplantation, or thermal ablation after a previously cured HCC, or HCC carcinoma with two unsuccessful rounds of transarterial chemoembolization • At least one untreated target lesion measured according to the RECIST <u>Exclusion criteria</u>: • Another primary tumour excluding BCC or superficial bladder cancer • Extrahepatic metastasis • Previous treatment of the current nodule • Active gastrointestinal bleeding or encephalopathy or refractory ascites • Any contraindication to hepatic embolisation <u>N total at baseline</u>: Intervention: 237 Control: 222 <u>Important prognostic factors</u>: Age, median (IQR):	weeks later. In bilobar tumours, the first treatment was delivered to the hemiliver with the greatest tumour burden and the contralateral hemiliver was scheduled for treatment 30–60 days after the first treatment. If the tumour progressed, SIRT could be repeated		deaths (n=5), medical decisions (n=3) Control: N=6 (2.7%) Reasons: patient choice (n=2), early deaths (n=2), medical decisions (n=2) <u>Incomplete outcome data</u>: Intervention: N=52 (23.0%) Reasons: did not meet inclusion criteria (n=8), received another anticancer treatment before progression (n=2), received sorafenib instead of SIRT (n=26), did not receive any treatment (n=16) Control: N=10 (4.5%) Reasons: did not meet inclusion criteria (n=8), received another anticancer treatment before progression (n=2)	HR 1.15 (95% CI 0.94-1.41) p=0.18 <u>Progression-free survival</u> Median PFS (months) I: 4.1 (95% CI 3.8-4.6) C: 3.7 (95% CI 3.3-5.4) HR 1.03 (95% CI 0.85-1.25) P=0.76 <u>Tumour response rate</u> I: 36/190 (19%), evaluable patients achieved a complete (n=5) or partial (n=31) response C: 23/198 (12%), evaluable patients achieved a complete (n=2) or partial (n=21) response <u>Adverse events</u> Grade ≥ 3 I: 92/226 (41%) C: 136/216 (63%) *A detailed record of all adverse*	longer in the SIRT group than in the sorafenib group • Many centres had little experience of administering SIRT <u>Authors conclusion:</u> "In patients with locally advanced or intermediate-stage hepatocellular carcinoma after unsuccessful transarterial chemoembolisation, overall survival did not significantly differ between the two groups. Quality of life and tolerance might help when choosing between the two treatments."

		I: 66 (60-72) C: 65 (58-73) Sex: I: 89.0% M C: 91.0% M Groups comparable at baseline? Yes				*events is reported in the article.* <u>Quality of life</u> Global health status subscore was significantly better in the SIRT group than in the sorafenib group (group effect p = 0.0048; time effect p < 0.0001) and the between-group difference tended to increase with time (group × time interaction p = 0.0447)	
Pereira, 2021 (SARAH)	See Vilgrain (2017)	See Vilgrain (2017) <u>N total at baseline</u>: Intervention: 174 Control: 206 <u>Important prognostic factors</u>: Age, median (IQR): I: 67 (61-72) C: 64 (57-71) Sex: I: 92.0% M C: 91.0% M	See Vilgrain (2017)	See Vilgrain (2017)	<u>Length of follow-up</u>: Minimum of 12 months or until death <u>Loss-to-follow-up & incomplete outcome data</u>: Intervention: N=52 (29.9 %) Reasons: no baseline assessment of QOL (n=24), no follow-up assessment of QOL (n=18), no baseline and follow-up assessment of QOL (n=10)	<u>Quality of life</u> Global health score at baseline: I: 65.3 (n=110) C: 65.1 (n=154) Global health score at 6 months I: 61.3 (n=57) C: 53.2 (n=77) Global health score at 12 months I: 63.5 (n=21) C: 54.1 (n=22)	<u>Auhors conclusion:</u> "HRQoL was preserved longer with TARE than with sorafenib in locally advanced HCC. These data could be used to optimise management of patients with advanced or inoperable HCC."

		Groups comparable at baseline? Yes			Control: N=43 (20.9%) Reasons: no baseline assessment of QOL (n=13), no follow-up assessment of QOL (n=24), no baseline and follow-up assessment of QOL (n=6)	Although there was a significant treatment effect (p = 0.006), and a significant time effect (p < 0.0001) on global health status, no treatment by time interaction was observed (p = 0.12).	

Risk of bias table

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** [a] Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?**[b] . Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?**[c] **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?**[d] Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?**[e] 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?**[f] Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure**[g] **LOW** **Some concerns** **HIGH**
Chow, 2018 (SIRveNIB)	Definitely yes Reason: Random assignment was performed through an	Probably no Reason: not reported	Definitely no Reason: open-label study	Definitely no Reason: More patients	Definitely yes Reason: Outcomes mentioned in the	Probably no Reason: Not all centers had facilities for the	Some concerns

	internet application at the patient level. Eligible patients were randomly assigned in a 1:1 ratio to receive either RE or sorafenib and stratified according to center and the presence or absence of portal vein thrombosis		Tumor response was assessed by a blinded reviewer.	randomly assigned to intervention than to sorafenib did not receive the assigned treatment (28.6% and 9%, respectively)	Methods section and at clinicaltrials.gov were reported in the article	radioembolization (RE). Patients from 11 participating countries had to travel to Singapore for their RE assessment. This delayed treatment initiation and, consequently, patients progressed, died, or withdrew consent before treatment. HRQoL was measured using the EQ-5D questionnaire, which is not a specific index for liver disease	
Vilgrain, 2017 (SARAH)	Definitely yes Reason: *"Eligible patients were randomly assigned (1:1) to receive either SIRT or sorafenib. The randomisation list was computer generated by the permutated block method with block sizes of two and four, and was stratified according to centre, ECOG performance status (0 versus 1), previous chemoembolisation (yes versus no), and presence of macroscopic vascular invasion (yes versus no)."*	Probably yes Reason: *"The funder, investigators, patients, and research staff remained masked to the randomisation list but were not masked to treatment."*	Definitely no Reason: open-label study	Definitely no Reason: More patients randomly assigned to intervention than to sorafenib did not receive the assigned treatment (23% and 4.5%, respectively)	Definitely yes Reason: Outcomes mentioned in the Methods section were reported. Secondary endpoints mentioned at clinicaltrials.gov were reported elsewhere (see Pereira et al. 2021 for QoL)	Probably no Reasons: Time between randomisation and treatment was much longer in the SIRT group than in the sorafenib group Many centers had little experience of administering SIRT	Some concerns
Pereira, 2021	See Vilgrain (2017)	See Vilgrain (2017)	See Vilgrain (2017)	See Vilgrain (2017)	Definitely yes	See Vilgrain (2017)	Some concerns

(SARAH)					Reason: Outcomes mentioned in the Methods section and at clinicaltrials.gov were reported in the article		

1. **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.**
2. **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.**
3. **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.**
4. **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.**
5. **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.**
6. **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.**
7. **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.**

Indicatoren

Bij deze module worden geen indicatoren ontwikkeld.

Kennislacunes

Kwaliteit van leven voor TARE versus systeemtherapie zou verder onderzocht moeten worden, daar is nu weinig literatuur over, waar het voor patiënten wel een belangrijke overweging is.

Evidence tables

Not applicable.

Table of excluded studies

Author and year	Reason for exclusion
Bouattour, 2017	Conference abstract
Finn, 2018	Does not add extra RCTs
Kim, 2019	Does not match PICO (patients)
Lemieux, 2021	Does not add extra RCTs
Ricke, 2019	Comparison not according to PICO
Wang, 2018	Does not add extra RCTs
Zou, 2019	Does not add extra RCTs

Literature search strategy

Algemene informatie

Richtlijn: NVMDL Hepatocellulair carcinoma	
Uitgangsvraag: UV8 SIRT/TARE versus systeemtherapie	
Database(s): Ovid/Medline, Embase	Datum: 15-4-2022
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.	

Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	142	34	157
RCTs	122	67	155
Observationele studies			
Overig			
Totaal			312

Zoekverantwoording

Embase

No.	Query	Results
#30	#27 NOT #29	**1**
#29	#27 AND #28	**3**
#28	#19 OR #20	**1475**
#27	#23 OR #24 OR #25 OR #26	**4**
#26	lemieux AND 2021 AND yttrium:ti	**1**
#25	personalised AND versus AND standard AND dosimetry AND approach AND of AND garin AND 2021	**1**

#24	sorafenib AND in AND 'asia pacific' AND patients AND chow AND 2018 AND sirvenib:ti NOT correlation:ti	**1**
#23	impact AND of AND combined AND sirt AND sorafenib AND on AND survival AND in AND ricke	**1**
#22	#21 NOT #20 RCT	**122**
#21	#8 AND #19	**163**
#20	#7 AND #19 SR	**142**
#19	#6 AND #18	**1475**
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	**2984688**
#17	'antineoplastic agent'/exp OR 'anticancerogen':ti,ab,kw OR 'antineoplastics':ti,ab,kw OR 'cancer chemotherapeutic agent':ti,ab,kw OR 'cancer inhibitor':ti,ab,kw OR 'tumor inhibitor':ti,ab,kw OR 'tumour inhibitor':ti,ab,kw OR 'anticarcinogen':ti,ab,kw OR antineoplastic:ti,ab,kw OR ((('anti cancer' OR anticancer OR antitumo?r OR carcinostat*) NEAR/3 (agent* OR drug* OR chemotherap* OR peptide*)):ti,ab,kw) OR ctla?4:ti,ab,kw	**2663201**
#16	'programmed death 1 ligand 1'/exp OR 'programmed death 1 receptor'/exp OR 'pd l1':ti,ab,kw	**68838**
#15	'protein tyrosine kinase inhibitor'/exp AND ((tyrosin* NEAR/2 kinase NEAR/2 inhibitor*):ti,ab,kw) OR 'vegfr inhibitor*':ti,ab,kw	**52194**
#14	'monoclonal antibody'/exp	**675585**
#13	'nivolumab'/exp OR 'bms 936558':ti,ab,kw OR 'bms936558':ti,ab,kw OR 'cmab 819':ti,ab,kw OR 'cmab819':ti,ab,kw OR 'mdx 1106':ti,ab,kw OR 'mdx1106':ti,ab,kw OR 'nivolumab':ti,ab,kw OR 'ono 4538':ti,ab,kw OR 'ono4538':ti,ab,kw OR 'opdivo':ti,ab,kw OR 'pembrolizumab'/exp OR 'keytruda':ti,ab,kw OR 'lambrolizumab':ti,ab,kw OR 'mk 3475':ti,ab,kw OR 'mk3475':ti,ab,kw OR 'pembrolizumab':ti,ab,kw OR 'sch 900475':ti,ab,kw OR 'sch900475':ti,ab,kw OR 'lenvatinib'/exp OR 'aiv 007':ti,ab,kw OR 'aiv007':ti,ab,kw OR 'e 7080':ti,ab,kw OR 'e7080':ti,ab,kw OR 'er 203492-00':ti,ab,kw OR 'er203492-00':ti,ab,kw OR 'kisplyx':ti,ab,kw OR 'lenvatinib':ti,ab,kw OR 'lenvima':ti,ab,kw OR 'mk 7902':ti,ab,kw OR 'mk7902':ti,ab,kw OR 'ramucirumab'/exp OR 'cyramza':ti,ab,kw OR 'imc 1121 b':ti,ab,kw OR 'imc 1121b':ti,ab,kw OR 'imc1121 b':ti,ab,kw OR 'imc1121b':ti,ab,kw OR 'ly 3009806':ti,ab,kw OR 'ly3009806':ti,ab,kw OR 'ramucirumab':ti,ab,kw OR 'regorafenib'/exp OR 'bay 73 4506':ti,ab,kw OR 'bay 734506':ti,ab,kw OR 'bay73 4506':ti,ab,kw OR 'bay734506':ti,ab,kw OR 'regorafenib':ti,ab,kw OR 'resihance':ti,ab,kw OR 'stivarga':ti,ab,kw	**50873**
#12	#10 AND #11	**2604**
#11	'bevacizumab'/exp OR 'abevmy':ti,ab,kw OR 'abp 215':ti,ab,kw OR 'abp215':ti,ab,kw OR 'ainex':ti,ab,kw OR 'altuzan':ti,ab,kw OR 'alymsys':ti,ab,kw OR 'ankeda':ti,ab,kw OR 'ask b1202':ti,ab,kw OR 'askb1202':ti,ab,kw OR 'avastin':ti,ab,kw OR 'aybintio':ti,ab,kw OR 'bat 1706':ti,ab,kw OR 'bat1706':ti,ab,kw OR 'bcd 021':ti,ab,kw OR 'bcd021':ti,ab,kw OR 'bevacizumab':ti,ab,kw OR 'bevax':ti,ab,kw OR 'bevz 92':ti,ab,kw OR 'bevz92':ti,ab,kw OR 'bi 695502':ti,ab,kw	**68167**

	OR 'bi695502':ti,ab,kw OR 'boyounuo':ti,ab,kw OR 'bryxta':ti,ab,kw OR 'byvasda':ti,ab,kw OR 'cbt 124':ti,ab,kw OR 'cbt124':ti,ab,kw OR 'chs 5217':ti,ab,kw OR 'chs5217':ti,ab,kw OR 'cizumab':ti,ab,kw OR 'ct p16':ti,ab,kw OR 'ctp16':ti,ab,kw OR 'equidacent':ti,ab,kw OR 'fkb 238':ti,ab,kw OR 'fkb238':ti,ab,kw OR 'gb 222':ti,ab,kw OR 'gb222':ti,ab,kw OR 'hd 204':ti,ab,kw OR 'hd204':ti,ab,kw OR 'hlx 04':ti,ab,kw OR 'hlx04':ti,ab,kw OR 'ibi 305':ti,ab,kw OR 'ibi305':ti,ab,kw OR 'jy 028':ti,ab,kw OR 'jy028':ti,ab,kw OR 'krabeva':ti,ab,kw OR 'kyomarc':ti,ab,kw OR 'lextemy':ti,ab,kw OR 'ly 01008':ti,ab,kw OR 'ly01008':ti,ab,kw OR 'mb 02':ti,ab,kw OR 'mb02':ti,ab,kw OR 'mil 60':ti,ab,kw OR 'mil60':ti,ab,kw OR 'mvasi':ti,ab,kw OR 'myl 14020':ti,ab,kw OR 'myl 1402o':ti,ab,kw OR 'myl14020':ti,ab,kw OR 'myl1402o':ti,ab,kw OR 'nsc 704865':ti,ab,kw OR 'nsc704865':ti,ab,kw OR 'onbevzi':ti,ab,kw OR 'ons 1045':ti,ab,kw OR 'ons 5010':ti,ab,kw OR 'ons1045':ti,ab,kw OR 'ons5010':ti,ab,kw OR 'oyavas':ti,ab,kw OR 'pf 06439535':ti,ab,kw OR 'pf 6439535':ti,ab,kw OR 'pf06439535':ti,ab,kw OR 'pf6439535':ti,ab,kw OR 'pusintin':ti,ab,kw OR 'ql 1101':ti,ab,kw OR 'ql1101':ti,ab,kw OR 'r 435':ti,ab,kw OR 'r435':ti,ab,kw OR 'rg 435':ti,ab,kw OR 'rg435':ti,ab,kw OR 'rhumab-vegf':ti,ab,kw OR 'ro 4876646':ti,ab,kw OR 'ro4876646':ti,ab,kw OR 'rph 001':ti,ab,kw OR 'rph001':ti,ab,kw OR 'sb 8':ti,ab,kw OR 'sb8':ti,ab,kw OR 'sct 510':ti,ab,kw OR 'sct510':ti,ab,kw OR 'stc 103':ti,ab,kw OR 'stc103':ti,ab,kw OR 'tab 008':ti,ab,kw OR 'tab008':ti,ab,kw OR 'tot 102':ti,ab,kw OR 'tot102':ti,ab,kw OR 'trs 003':ti,ab,kw OR 'trs003':ti,ab,kw OR 'tx 16':ti,ab,kw OR 'tx16':ti,ab,kw OR 'versavo':ti,ab,kw OR 'zirabev':ti,ab,kw OR 'zrc 113':ti,ab,kw OR 'zrc113':ti,ab,kw	
#10	'atezolizumab'/exp OR 'atezolizumab':ti,ab,kw OR 'mpdl 3280a':ti,ab,kw OR 'mpdl3280a':ti,ab,kw OR 'rg 7446':ti,ab,kw OR 'rg7446':ti,ab,kw OR 'ro 5541267':ti,ab,kw OR 'ro5541267':ti,ab,kw OR 'tecentriq':ti,ab,kw OR 'tecntriq':ti,ab,kw	**10482**
#9	impact AND of AND combined AND sirt AND sorafenib AND on AND survival AND in AND ricke	**1**
#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	**1900030**
#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	**733409**

	(review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
#6	#5 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)	**3482**
#5	#3 AND #4	**7548**
#4	'liver cell carcinoma'/exp OR 'liver tumor'/exp OR (((hepat* OR liver) NEAR/3 (carcinom* OR cancer* OR neoplasm* OR malignan*)):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw OR (((primary OR second*) NEAR/2 liver):ti,ab,kw)	**393579**
#3	#1 OR #2	**64882**
#2	'microsphere'/exp/mj OR 'microsphere':ti,ab,kw OR 'yttrium 90'/exp OR '90 y':ti,ab,kw OR yttrium:ti,ab,kw OR '90y':ti,ab,kw OR 'y 90':ti,ab,kw OR 'y90':ti,ab,kw OR 'radioyttrium':ti,ab,kw OR 'radioactive yttrium':ti,ab,kw OR 'yttrium'/exp	**45481**
#1	'selective internal radiotherapy'/exp OR 'radioembolization'/exp/mj OR 'radioemboli?ation':ti,ab,kw OR tare:ti,ab,kw OR 'selective internal radiation therapy'/exp OR sirt:ti,ab,kw	**7769**

Ovid/Medline

#	Searches	Results
16	15 not 14 RCT	68
15	6 and 13	86
14	5 and 13 SR	34
13	4 and 12	541
12	7 or 8 or 9 or 10 or 11	1428291
11	Programmed Cell Death 1 Receptor/ or pd l1.ti,ab,kf.	25667
10	Antibodies, Monoclonal/ or (tyrosin* adj2 kinase adj2 inhibitor*).ti,ab,kf. or vegfr inhibitor*.ti,ab,kf.	230636
9	exp nivolumab/ or bms 936558.ti,ab,kf. or bms936558.ti,ab,kf. or cmab 819.ti,ab,kf. or cmab819.ti,ab,kf. or mdx 1106.ti,ab,kf. or mdx1106.ti,ab,kf. or nivolumab.ti,ab,kf. or ono 4538.ti,ab,kf. or ono4538.ti,ab,kf. or opdivo.ti,ab,kf. or keytruda.ti,ab,kf. or lambrolizumab.ti,ab,kf. or mk 3475.ti,ab,kf. or mk3475.ti,ab,kf. or pembrolizumab.ti,ab,kf. or sch 900475.ti,ab,kf. or sch900475.ti,ab,kf. or "aiv 007".ti,ab,kf. or aiv007.ti,ab,kf. or e 7080.ti,ab,kf. or e7080.ti,ab,kf. or er 203492-00.ti,ab,kf. or er203492-00.ti,ab,kf. or kisplyx.ti,ab,kf. or lenvatinib.ti,ab,kf. or lenvima.ti,ab,kf. or mk 7902.ti,ab,kf. or mk7902.ti,ab,kf. or cyramza.ti,ab,kf. or imc 1121 b.ti,ab,kf. or imc 1121b.ti,ab,kf. or imc1121 b.ti,ab,kf. or imc1121b.ti,ab,kf. or ly 3009806.ti,ab,kf. or ly3009806.ti,ab,kf. or ramucirumab.ti,ab,kf. or bay	15055

	73 4506.ti,ab,kf. or bay 734506.ti,ab,kf. or bay73 4506.ti,ab,kf. or bay734506.ti,ab,kf. or regorafenib.ti,ab,kf. or resihance.ti,ab,kf. or stivarga.ti,ab,kf.	
8	(atezolizumab or mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or ro 5541267 or ro5541267 or tecentriq or tecntriq).ti,ab,kf. and (exp Bevacizumab/ or abevmy.ti,ab,kf. or abp 215.ti,ab,kf. or abp215.ti,ab,kf. or ainex.ti,ab,kf. or altuzan.ti,ab,kf. or alymsys.ti,ab,kf. or ankeda.ti,ab,kf. or ask b1202.ti,ab,kf. or askb1202.ti,ab,kf. or avastin.ti,ab,kf. or aybintio.ti,ab,kf. or bat 1706.ti,ab,kf. or bat1706.ti,ab,kf. or "bcd 021".ti,ab,kf. or bcd021.ti,ab,kf. or bevacizumab.ti,ab,kf. or bevax.ti,ab,kf. or bevz 92.ti,ab,kf. or bevz92.ti,ab,kf. or bi 695502.ti,ab,kf. or bi695502.ti,ab,kf. or boyounuo.ti,ab,kf. or bryxta.ti,ab,kf. or byvasda.ti,ab,kf. or cbt 124.ti,ab,kf. or cbt124.ti,ab,kf. or chs 5217.ti,ab,kf. or chs5217.ti,ab,kf. or cizumab.ti,ab,kf. or ct p16.ti,ab,kf. or ctp16.ti,ab,kf. or equidacent.ti,ab,kf. or fkb 238.ti,ab,kf. or fkb238.ti,ab,kf. or gb 222.ti,ab,kf. or gb222.ti,ab,kf. or hd 204.ti,ab,kf. or hd204.ti,ab,kf. or "hlx 04".ti,ab,kf. or hlx04.ti,ab,kf. or ibi 305.ti,ab,kf. or ibi305.ti,ab,kf. or "jy 028".ti,ab,kf. or jy028.ti,ab,kf. or krabeva.ti,ab,kf. or kyomarc.ti,ab,kf. or lextemy.ti,ab,kf. or "ly 01008".ti,ab,kf. or ly01008.ti,ab,kf. or "mb 02".ti,ab,kf. or mb02.ti,ab,kf. or mil 60.ti,ab,kf. or mil60.ti,ab,kf. or mvasi.ti,ab,kf. or myl 14020.ti,ab,kf. or myl 1402o.ti,ab,kf. or myl14020.ti,ab,kf. or myl1402o.ti,ab,kf. or nsc 704865.ti,ab,kf. or nsc704865.ti,ab,kf. or onbevzi.ti,ab,kf. or ons 1045.ti,ab,kf. or ons 5010.ti,ab,kf. or ons1045.ti,ab,kf. or ons5010.ti,ab,kf. or oyavas.ti,ab,kf. or "pf 06439535".ti,ab,kf. or pf 6439535.ti,ab,kf. or pf06439535.ti,ab,kf. or pf6439535.ti,ab,kf. or pusintin.ti,ab,kf. or ql 1101.ti,ab,kf. or ql1101.ti,ab,kf. or r 435.ti,ab,kf. or r435.ti,ab,kf. or rg 435.ti,ab,kf. or rg435.ti,ab,kf. or rhumab-vegf.ti,ab,kf. or ro 4876646.ti,ab,kf. or ro4876646.ti,ab,kf. or "rph 001".ti,ab,kf. or rph001.ti,ab,kf. or sb 8.ti,ab,kf. or sb8.ti,ab,kf. or sct 510.ti,ab,kf. or sct510.ti,ab,kf. or stc 103.ti,ab,kf. or stc103.ti,ab,kf. or "tab 008".ti,ab,kf. or tab008.ti,ab,kf. or tot 102.ti,ab,kf. or tot102.ti,ab,kf. or "trs 003".ti,ab,kf. or trs003.ti,ab,kf. or tx 16.ti,ab,kf. or tx16.ti,ab,kf. or versavo.ti,ab,kf. or zirabev.ti,ab,kf. or zrc 113.ti,ab,kf. or zrc113.ti,ab,kf.)	374
7	exp Antineoplastic Agents/ or anticancerogen.ti,ab,kf. or antineoplastics.ti,ab,kf. or cancer chemotherapeutic agent.ti,ab,kf. or cancer inhibitor.ti,ab,kf. or tumor inhibitor.ti,ab,kf. or tumour inhibitor.ti,ab,kf. or anticarcinogen.ti,ab,kf. or antineoplastic.ti,ab,kf. or ((anti cancer or anticancer or antitumo?r or carcinostat*) adj3 (agent* or drug* or chemotherap* or peptide*)).ti,ab,kf. or ctla?4.ti,ab,kf.	1233681
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.) not (animals/ not humans/)	1367010
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 literature or	558807

	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/))	
4	3 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	2046
3	1 and 2	2279
2	exp Yttrium/ or exp Yttrium Radioisotopes/ or exp Microspheres/ or radioemboli?at*.ti,ab,kf. or tare.ti,ab,kf. or sirt.ti,ab,kf. or (sele?t* adj3 (radiati* or radiotherap*)).ti,ab,kf. or yttrium.ti,ab,kf. or microsphere*.ti,ab,kf. or 90 y.ti,ab,kf. or 90y.ti,ab,kf. or y 90.ti,ab,kf. or y90.ti,ab,kf.	64915
1	Carcinoma, Hepatocellular/ or (hepat* adj3 carcinom*).ti,ab,kf. or hepatocarcinom*.ti,ab,kf. or hepatoma.ti,ab,kf. or (liver adj3 primary).ti,ab,kf.	162623

Module 9 Beeldvorming of histologie

Uitgangsvraag

Wat is de rol van beeldvorming (dat wil zeggen MRI of CT) bij patiënten verdacht van een levertumor zonder bekende levercirrose?

Inleiding

Niet-invasieve diagnostiek middels beeldvorming (CT/MRI) van hepatocellulair carcinoom (HCC) bij een niet-cirrotische lever is veel minder specifiek dan bij een cirrotische lever. Om deze reden wordt tot dusver een tumor biopt van de laesie geadviseerd bij verdenking HCC in patiënt met een niet-cirrotische lever. In de beeldvorming zijn continu ontwikkelingen gaande qua techniek, software, resolutie en andere mogelijkheden om weefsel te karakteriseren. In deze zoekvraag wordt de accuratesse van beeldvorming vergeleken met histologie voor het stellen van de diagnose HCC bij patiënten zonder levercirrose.

Search and select

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

What is the diagnostic accuracy of MRI or a multiphasic CT-scan in patients suspected of a hepatocellular carcinoma with or without liver disease, but excluding liver cirrhosis, compared to histology as a reference standard?

P: patients suspected of a hepatocellular carcinoma without other liver disease and/or with liver disease excluding cirrhosis;
I: MRI or multiphasic CT-scan;
C: -;
R: Histology;
O: Sensitivity, specificity, positive predictive value, negative predictive value.

Relevant outcome measures

The guideline development group considered unequivocal diagnosis of hepatocellular carcinoma (HCC), sensitivity, and negative predictive value as a critical outcome measure for decision making; and suspicion for HCC as an important outcome measure for decision making.

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

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 21-07-2022 for systematic reviews. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 33 unique hits. Studies were selected based on the following criteria: patients were suspected of a hepatocellular carcinoma, patients either did not have other liver disease or had liver disease excluding cirrhosis, MRI or a multiphasic CT-scan was used as an index test, histology was used as a reference standard, at least one of the outcomes of interest was reported or could be calculated from the presented data, and the article was a systematic review. Ten systematic revies were selected based on title and abstract screening. After reading the full text, all systematic reviews were excluded (see the table with reasons for exclusion under the tab Methods).

Since no relevant aggregated evidence seemed to be available, we used the title and abstract selection of two recent Cochrane reviews about detecting HCCs with CT and MRI (Nadarevic, 2021; Nadarevic, 2022), which both were identified in our search strategy. We downloaded the study data from the included studies in the Cochrane reviews through the Cochrane Library and identified and read those studies with a prevalence of cirrhosis either not reported or being <100% in full text for our study selection (n=12 studies). These studies could potentially report (sub-)analyses for patients with non-cirrhotic livers. Thus, twelve primary studies originally included in the Cochrane reviews were read full-text of which we excluded ten studies (see the table with reasons for exclusion under the tab Methods). We furthermore screened 214 excluded articles (after removing duplicates) by Nadarevic (2021, 2022) on the title and abstract for potentially relevant studies for the current guideline module. Eighteen primary studies were selected based on title and abstract screening, from which seventeen studies were excluded (see the table with reasons for exclusion under the tab Methods). This method resulted in the selection of three primary studies.

Results

Three primary studies were included in the analysis of the literature (Fischer, 2015; Kim, 2011; Lin, 2016). 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

Fischer (2015) recruited 107 consecutive patients from five centers suspected of a hepatocellular carcinoma without liver cirrhosis. Patients were included when they had an MRI prior to surgery for a suspicious HCC lesion, had histopathological evidence of HCC, had histopathological evidence of a non-cirrhotic liver, and when time between MRI and surgery was less than 2 months. Exclusion criteria did not seem to be described. Prevalence of HCC was 51.4%. The cohortconsisted of 46 males and 61 females. HBV status for patients with benign lesions was negative (n=43), positive (n=1), or unknown (n=8), while for HCC lesions this was n=40, n=11, and n=4 in the respective categories. In patients with benign lesions the HCV status was negative (n=44), positive (n=0), or unknown (n=8), and in patients with HCC lesions this was n=47 (negative), n=4 (positive), and n=4 (unclear). Median AFP in the patients with benign lesions was 2.3 (IQR: 1.5 to 4.0) and 3.5 (IQR 2.7 to 7.4) for patients with HCC. The five centers used different MR sequences in the axial and/or coronal plane (i.e. T1 Dyn lava, T1 flash FS, T1 flash in/opp, T1 in/opp, T1 vibe 3D dynamic ,T2 blade (TSE), T2 FRFSE, T2 FS RT, T2 SSFSE, T2 SSFSH, T2 trufi, T2 TSE, T2Haste, T2Haste fat sat). Time of repetition (range: 3.3 to 9474), time of echo (range: 1.3 to 105), flip angle (range: 15 to 180), and slice thickness (range: 3 to 10) parameters were reported. LI-RADS were used for diagnosis. Three imaging protocols were used: single contrast with an extracellular agent (n=53), single contrast with a hepatobiliary-specific agent (n=42), and a double contrast protocol with ECF and reticuloendothelial-specific agents (n=12). The surgical specimen underwent standard histopathological examination.

Kim (2011) prospectively enrolled patients between December 2006 and June 2009 with hepatic masses larger than 2 centimeters who were admitted at the hepatology department of a single center (Asan Medical Center, Korea). Other inclusion criteria did not seem to be described. Patients with hepatic nodules between 1 and 2 centimeters were excluded (n=68), had received a CT as staging work-up for a known primary extrahepatic malignancy, were in the terminal stage of the disease, had severe coagulopathy and/or had intraperitoneal bleeding from spontaneously ruptured tumors. The reference standard was fine needle biopsy under ultrasound guidance and diagnosis was set according to the

International Working Party criteria. At least two liver tissue cores were obtained from each patient and stained with hematoxylin-eosin. A second fine needle biopsy was performed when the first was inconclusive. Patients with inconclusive results from the fine needle biopsies were excluded from analyses. Eleven patients refused a second fine needle biopsy and were excluded from the analyses. Patients with AFP>200ng/ml or typical enhancement pattern and with risk factors for HCC were candidates for surgical resection and did not undergo fine needle biopsies (n=24). Patients underwent a helical CT-scan with 4 phases (non-contrast, arterial, portal, delayed) with both a slice thickness and table feed of 5 millimeters. Iopromide was used as a nonionic contrast agent (120ml, 3.5ml/sec via power injector). Scanning delay was determined using SmartPrep. Arterial phase, portal phase, and delayed phase respectively began at 24, 72-90, and 180 seconds after the aortic enhancement reached 100HU above the pre-contrast attenuation. CT findings were read by two radiologists having 10 and 20 years experience in liver imaging, respectively. Hypervascular enhancement (arterial phase) and washout (portal/delayed phase) were classified as typically vascular. Tumors with mixed areas of hypervascularity (area >70%) and hypovascularity were considered a typical enhancement pattern. Other patterns were considered atypical. The sample was divided into three groups: patients with cirrhosis (n=107), high risk patients without cirrhosis (positive for hepatitis B surface antigen and/or anti-HCV, n=62), and low risk patients without cirrhosis (negative for hepatitis B surface antigen and/or anti-HCV, n=37). The high risk patients (n=52 males, n= 10 females) had a median age of 52 years (range: 30 to 71). Hepatitis status in the high risk group was positive for hepatitis B (n=56), positive for hepatitis C (n=5, or positive for both hepatitis B and C (n=1). Low risk patients (n=21 males, n=16 females) had a median age of 52 years (range: 23 to 81) and all had no or cryptogenic underlying liver disease.

Lin (2016) conducted a retrospective study in Taiwan. Patients that had undergone a tumor resection or liver transplantation between January 2006 and October 2010 in the Chang Gang Memorial Hospital were selected. Other inclusion criteria did not seem to be described. Patients without a liver CT or MRI before surgery, without available pathological fibrosis score, or without a tumor in the explanted liver were excluded. Selected patients (n=841) underwent CT (n=756) and/or MRI (n=204). HCC imaging characteristics were defined as early enhancement in the arterial phase and early washout in the venous phase. The reference tests were histological and surgical reports. Patients who underwent CT (n =555 males, n =201 females) had a mean age of 55.81 years (SD: 12.27) and the mean tumor size was 5.44cm (SD: 4.12; 1-2cm: n=131, >2cm: n=625). Pathological METAVIR fibrosis score was F0 (n=104), F1 (n=88), F2 (n=40), F3 (n=77), or F4 (n=281, chirrosis). Hepatitis-status in the CT-group was: non hepatitis B or C (n=202), hepatitis B (n=374), hepatitis C (n=157), or hepatitis B and C (n=22). A helical CT with 4 phases was performed (non-contrast, arterial, portal, and delayed) and the scan was acquired in a clockwise direction in 5mm sections. Contrast medium (2ml/sec, 80ml total) was used, although it did not seem to be reported which contrast medium was used. The scan for the arterial phase started 30 seconds after injection with the contrast medium. The scan for the portal phase started 20 seconds after the arterial phase, and the scan for the venous phase started 20 seconds after the portal phase. Patients who received an MRI (n=142 males, n=62 females) had a mean age of 54 years (SD: 12.49) and a mean tumor size of 4.04cm (SD: 3.13; 1-2cm: n=58, >2cm: n=146). The pathological METAVIR fibrosis score for patients who received an MRI was F0 (n=21), F1 (n=18), F2 (n=2), F3 (n=14), or F4 (n=90, cirrhosis). MR imaging was acquired using 1.5-2T MRI including contrast medium (Gd-DTPA, 0.2mg/kg, 1.6-1.8ml/sec) using T1WI, T2WI, T2WI Fsat, heavy T2WI, long T2WI, and/or enhanced T1WI pulse sequences (8mm thickness, 2mm gap) in three phases. The first phase was obtained 15 seconds after the contrast infusion, while the second and third phase were obtained after 30 second intervals.

Results

Computed Tomography Scan

Sensitivity

Kim (2011) reported the sensitivity of CT for HCCs in hepatic nodules >2cm in patients without cirrhosis and divided this group in high risk and low risk groups for HCC. The sensitivity of CT in the high-risk group was 81.6% (95%CI: 0.67 to 0.91, n=49), while the sensitivity in the low-risk group was 87.5% (95%CI: 0.60 to 0.98, n=16).

Lin (2016) reported the sensitivity of CT for HCCs in a non-cirrhotic sample. The sensitivity was calculated depending on the increasing METAVIR fibrosis scores and the size of the HCC. Figures 9.1 and 9.2 summarize the sensitivities for detecting HCCs (1-2cm and >2cm respectively) with CT.

Specificity

Kim (2011) reported the specificity of CT for HCCs in hepatic nodules >2cm in a group of high-risk patients without cirrhosis and in a group with low-risk patients without cirrhosis. The specificity of CT in the high-risk group was 92.3% (95%CI: 0.62 to 0.99, n=13), while the specificity in the low-risk group was 90.5% (95%CI: 0.68 to 0.98, n=21).

Lin (2016) reported the specificity of CT for HCCs in a non-cirrhotic sample. The specificity was calculated depending on the increasing METAVIR fibrosis scores and the size of the HCC. Figures 1 and 2 summarize the specificities for detecting HCCs (1-2cm and >2cm respectively) with CT.

Figure 9.1 – Sensitivity and specificity of CT detecting 1-2cm HCCs depending on the METAVIR fibrosis scores in the sample, from Lin (2016). A score from F0 to F3 means cirrhosis is absent but fibrosis is increasingly present. (TP: True Positive, FP: False Positive, FN: False negative, TN: True Negative, CI: Confidence interval)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lin 2016 F0 (1-2cm)	5	0	2	1	0.71 [0.29, 0.96]	1.00 [0.03, 1.00]
Lin 2016 F0-1 (1-2cm)	11	1	7	1	0.61 [0.36, 0.83]	0.50 [0.01, 0.99]
Lin 2016 F0-2 (1-2cm)	14	1	7	1	0.67 [0.43, 0.85]	0.50 [0.01, 0.99]
Lin 2016 F0-3 (1-2cm)	30	5	8	18	0.79 [0.63, 0.90]	0.78 [0.56, 0.93]

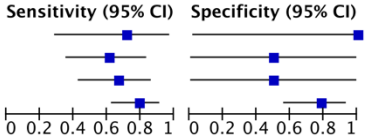
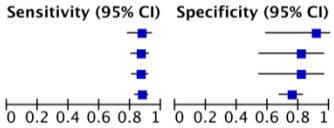


Figure 9.2 – Sensitivity and specificity of CT detecting HCCs >2cm depending on the METAVIR fibrosis scores in the sample, from Lin (2016). A score from F0 to F3 means cirrhosis is absent but fibrosis is increasingly present. (TP: True Positive, FP: False Positive, FN: False negative, TN: True Negative, CI: Confidence interval)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lin 2016 F0 (larger than 2cm)	74	1	11	10	0.87 [0.78, 0.93]	0.91 [0.59, 1.00]
Lin 2016 F0-1 (larger than 2cm)	135	3	21	13	0.87 [0.80, 0.91]	0.81 [0.54, 0.96]
Lin 2016 F0-2 (larger than 2cm)	166	3	26	13	0.86 [0.81, 0.91]	0.81 [0.54, 0.96]
Lin 2016 F0-3 (larger than 2cm)	239	35	35	107	0.87 [0.83, 0.91]	0.75 [0.67, 0.82]



Positive predictive value

Kim (2011) reported the positive predictive value of CT in both the high-risk group without chirrosis (PPV: 97.6%, 95%CI: 0.86 to 0.99) and the low-risk group without cirrhosis (PPV: 87.5%, 95%CI: 0.60 to 0.98).

Lin (2016) calculated the positive predictive values of CT detecting both 1-2cm and >2cm HCCs, respectively. Results are summarized in Table 9.3.

Negative predictive value

Kim (2011) reported the negative predictive value of CT in both in the high-risk group without cirrhosis and in the low-risk group without cirrhosis. CT in the high-risk group had a negative predictive value of 57.1% (95%CI: 0.34 to 0.77), while this was 90.4% (95%CI: 0.68 to 0.98) in the low-risk group.

Lin (2016) calculated the negative predictive values of CT detecting both 1-2cm and >2cm HCCs, respectively. Results are summarized in Table 9.3.

Table 9.3 – Positive and negative predictive values of CT on the size of the HCC and METAVIR-score in the sample, from Lin (2016). Confidence intervals were calculated in RevMan 5. A score from F0 to F3 means cirrhosis is absent but fibrosis is increasingly present.

	CT	
	PPV (95%CI)	**NPV (95%CI)**
1-2cm HCC		
METAVIR F0	100% (0.48-1.00)‡	33.3% (0.01-0.91)‡
METAVIR F0-1	91.7% (0.62-1.00)†	12.5% (0.00-0.53)‡
METAVIR F0-2	87.5% (0.62-0.98)†	12.5% (0.00-0.53)‡
METAVIR F0-3	85.7% (0.70-0.95)†	69.2% (0.48-0.86)†
>2cm HCC		
METAVIR F0	98.7% (0.93-1.00)*	38.2% (0.26-0.70)†
METAVIR F0-1	97.8% (0.95-1.00)	38.2% (0.22-0.56)†
METAVIR F0-2	98.2% (0.95-1.00)	33.3% (0.19-0.50)†
METAVIR F0-3	89.5% (0.85-0.93)	75.4% (0.67-0.82)

* Calculation in a (sub)sample with between 50-100 patients
† Calculation in a (sub)sample with between 10-50 patients
‡ Calculation in a (sub)sample with less than 10 patients
CI: Confidence Interval
Cm: centimeters
CT: Computed Tomography
HCC: Hepatocellular Carcinoma
NPV: Negative Predictive Value
PPV: Positive Predictive Value

Magnetic Resonance Imaging

Sensitivity

Fischer (2015) identified four MR features associated with HCC in patients with non-cirrhotic livers and reported their sensitivity:

- T1-intensity (hypointense): 0.78 (95%CI: 0.65-0.88).
- T2-intensity (not isointense): 0.85 (95%CI: 0.73-0.94).
- Central enhancement (no): 0.69 (95%CI: 0.55-0.81).
- Satellite lesions (yes): 0.24 (95%CI: 0.13-0.37).

The 95%CI's were recalculated in RevMan 5. When combined, any two positive features of the four resulted in a sensitivity of 0.91 (95%CI not reported and could not be calculated).

Lin (2016) reported the sensitivity of MRI for HCCs in patients with a non-cirrhotic liver. The specificity was calculated depending on the increasing METAVIR fibrosis scores and the size of the HCC. Figures 3 and 4 summarize the sensitivities for detecting HCCs (1-2cm and >2cm, respectively) with MRI.

Specificity

The specificity of the four MR features identified by Fischer (2015) having an association with HCC in patients with non-cirrhotic livers was reported:

- T1-intensity (hypointense): 0.63 (95%CI: 0.49-0.76).
- T2-intensity (not isointense): 0.50 (95%CI: 0.36-0.64).
- Central enhancement (no): 0.73 (95%CI: 0.59-0.84).
- Satellite lesions (yes): 0.96 (95%CI: 0.87-1.00).

The 95%CIs were recalculated in RevMan 5. When combined, any two positive features of the four resulted in a specificity of 0.75. When all four features were positive, specificity reached 0.98. The confidence intervals were not reported.

Lin (2016) reported the specificity of MRI for detecting HCCs in patients without liver cirrhosis. The specificity was calculated depending on the increasing METAVIR fibrosis scores and the size of the HCC. See Figures 9.4 and 9.5 for a summary of the specificities for MRI detecting HCCs (1-2cm and >2cm, respectively).

Figure 9.4 – Sensitivity and specificity of MRI detecting 1-2cm HCCs depending on the METAVIR fibrosis scores in the sample, from Lin (2016). A score from F0 to F3 means cirrhosis is absent but fibrosis is increasingly present. (TP: True Positive, FP: False Positive, FN: False negative, TN: True Negative, CI: Confidence interval)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lin 2016 F0 (1–2cm)	1	0	0	1	1.00 [0.03, 1.00]	1.00 [0.03, 1.00]
Lin 2016 F0–1 (1–2cm)	2	0	1	1	0.67 [0.09, 0.99]	1.00 [0.03, 1.00]
Lin 2016 F0–2 (1–2cm)	2	0	1	1	0.67 [0.09, 0.99]	1.00 [0.03, 1.00]
Lin 2016 F0–3 (1–2cm)	5	2	1	8	0.83 [0.36, 1.00]	0.80 [0.44, 0.97]

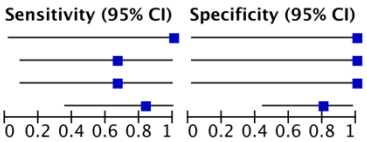
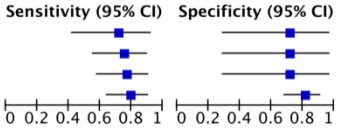


Figure 9.5 – Sensitivity and specificity of MRI detecting HCCs >2cm depending on the METAVIR fibrosis scores in the sample, from Lin (2016). A score from F0 to F3 means cirrhosis is absent but fibrosis is increasingly present. (TP: True Positive, FP: False Positive, FN: False negative, TN: True Negative, CI: Confidence interval)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lin 2016 F0 (larger than 2cm)	10	2	4	5	0.71 [0.42, 0.92]	0.71 [0.29, 0.96]
Lin 2016 F0–1 (larger than 2cm)	21	2	7	5	0.75 [0.55, 0.89]	0.71 [0.29, 0.96]
Lin 2016 F0–2 (larger than 2cm)	23	2	7	5	0.77 [0.58, 0.90]	0.71 [0.29, 0.96]
Lin 2016 F0–3 (larger than 2cm)	34	10	9	43	0.79 [0.64, 0.90]	0.81 [0.68, 0.91]



Positive predictive value

Fischer (2015) reported the positive predictive values of four MR imaging features:

- T1-intensity (hypointense): 0.69 (95%CI: 0.57-0.81).
- T2-intensity (not isointense): 0.64 (95%CI: 0.52-0.76).
- Central enhancement (no): 0.73 (95%CI: 0.60-0.86).
- Satellite lesions (yes): 0.87 (95%CI: 0.66-1.00).

Lin (2016) calculated the positive predictive values of MRI detecting both 1-2cm and >2cm HCCs, respectively. Results are summarized in Table 2.

Negative predictive value

Fischer (2015) reported the negative predictive values of four MR imaging features:

- T1-intensity (hypointense): 0.73 (95%CI: 0.59-0.87).
- T2-intensity (not isointense): 0.76 (95%CI: 0.60-0.92).
- Central enhancement (no): 0.69 (95%CI: 0.55-0.82).
- Satellite lesions (yes): 0.54 (95%CI: 0.43-0.65).

Lin (2016) calculated the negative predictive values of MRI detecting both 1-2cm and >2cm HCCs, respectively. Results are summarized in Table 9.6.

Table 9.6 – Positive and negative predictive values of MRI depending on the size of the HCC and METAVIR-score in the sample, from Lin (2016). Confidence intervals were calculated in RevMan 5. A score from F0 to F3 means cirrhosis is absent but fibrosis is increasingly present.

	MRI	
	PPV (95%CI)	**NPV (95%CI)**
1-2cm HCC		
METAVIR F0	100% (0.03-1.00)‡	100% (0.03-1.00)‡
METAVIR F0-1	100% (0.16-1.00)‡	50% (0.01-0.99)‡
METAVIR F0-2	100% (0.16-1.00)‡	50% (0.01-0.99)‡
METAVIR F0-3	71.4% (0.29-0.96)‡	88.9% (0.52-1.00)‡

>2cm HCC		
METAVIR F0	90.9% (0.62-0.89)†	50% (0.16-0.84)‡
METAVIR F0-1	91.3% (0.72-0.99)†	41.7% (0.15-0.72)†
METAVIR F0-2	92% (0.74-0.99)†	41.7% (0.15-0.72)†
METAVIR F0-3	77.3% (0.62-0.89)†	82.7% (0.70-0.92)*

* Calculation in a (sub)sample with between 50-100 patients
† Calculation in a (sub)sample with between 10-50 patients
‡ Calculation in a (sub)sample with less than 10 patients
CI: Confidence Interval
Cm: centimeters
HCC: Hepatocellular Carcinoma
MRI: Magnetic Resonance Imaging
NPV: Negative Predictive Value
PPV: Positive Predictive Value

Level of evidence of the literature

Computed Tomography scan

The level of evidence regarding the outcome measure sensitivity was downgraded by 1 level because of study limitations (1 level for risk of bias: Nadarevic (2021, 2022) judged both studies to have high risk of bias on patient selection, flow and timing, and one study also on the reference standard); number of included patients (0 to -2 levels for imprecision: wide to very wide confidence intervals depending on the subgrouping in analysis; 1-2cm HCC's are more imprecise and may warrant a -2 for imprecision); publication bias was not assessed.

The level of evidence regarding the outcome measure specificity was downgraded by 3 levels because of study limitations (1 level for risk of bias: Nadarevic (2021, 2022) judged both studies to have high risk of bias on patient selection, flow and timing, and one study also on the reference standard); number of included patients (2 levels for imprecision: very wide confidence intervals); publication bias was not assessed.

The level of evidence regarding the outcome measure positive predictive value was downgraded by 2 levels because of study limitations (1 level for risk of bias: Nadarevic (2021, 2022) judged both studies to have high risk of bias on patient selection, flow and timing, and one study also on the reference standard); number of included patients (1 level for imprecision: wide to very wide confidence intervals depending on the subgrouping in analysis; 1-2cm HCC's are more imprecise and may warrant a -2 for imprecision); publication bias was not assessed.

The level of evidence regarding the outcome measure negative predictive value was downgraded by 3 levels because of study limitations (1 level for risk of bias: Nadarevic (2021, 2022) judged both studies to have high risk of bias on patient selection, flow and timing, and one study also on the reference standard); number of included patients (2 levels for imprecision: very wide confidence intervals); publication bias was not assessed.

Magnetic Resonance Imaging

The level of evidence regarding the outcome measure sensitivity was downgraded by 3 levels because of study limitations (1 level for risk of bias: one of the two studies (carrying about 50% of the sample size in the body of evidence) was judged to have a high risk of bias for patient selection and flow and timing by Nadarevic (2022)); number of included patients (2 levels for imprecision: very wide confidence intervals); publication bias was not assessed.

The level of evidence regarding the outcome measure specificity was downgraded by 3 levels because of study limitations (1 level for risk of bias: one of the two studies (carrying about 50% of the sample size in the body of evidence) was judged to have a high risk of bias

for patient selection and flow and timing by Nadarevic (2022)); number of included patients (2 levels for imprecision: very wide confidence intervals); publication bias was not assessed.

The level of evidence regarding the outcome measure positive predictive value was downgraded by 3 levels because of study limitations (1 level for risk of bias: one of the two studies (carrying about 50% of the sample size in the body of evidence) was judged to have a high risk of bias for patient selection and flow and timing by Nadarevic (2022)); number of included patients (2 levels for imprecision: very wide confidence intervals); publication bias was not assessed.

The level of evidence regarding the outcome measure negative predictive value was downgraded by 3 levels because of study limitations (1 level for risk of bias: one of the two studies (carrying about 50% of the sample size in the body of evidence) was judged to have a high risk of bias for patient selection and flow and timing by Nadarevic (2022)); number of included patients (2 levels for imprecision: very wide confidence intervals); publication bias was not assessed.

Conclusions

Computed tomography scan

Moderate GRADE	There is a moderate certainty in the reported sensitivity of computed tomography in patients with a hepatocellular carcinoma measuring over 2 centimeters and with or without other liver disease, excluding liver cirrhosis. The certainty in the reported sensitivity may be very low for patients with a hepatocellular carcinoma measuring 1-2 centimeters and with or without other liver disease, excluding liver cirrhosis. *Sources: (Kim, 2011; Lin, 2016)*

Very low GRADE	There is a very low certainty in the reported specificity of computed tomography in patients with a hepatocellular carcinoma with or without other liver disease, excluding liver cirrhosis. *Sources: (Kim, 2011; Lin, 2016)*

Low GRADE	There is a low certainty in the reported positive predictive value of computed tomography in patients with a hepatocellular carcinoma measuring over 2 centimeters and with or without other liver disease, excluding liver cirrhosis. The certainty may be very low for patients with a hepatocellular carcinoma measuring 1-2 centimeters and with or without other liver disease, excluding liver cirrhosis. *Sources: (Kim, 2011; Lin, 2016)*

Very low GRADE	There is a very low certainty in the reported negative predictive value of computed tomography in patients with a hepatocellular carcinoma with or without other liver disease, excluding liver cirrhosis. *Sources: (Kim, 2011; Lin, 2016)*

Magnetic Resonance imaging

Very low GRADE	There is a very low certainty in the reported sensitivity of magnetic resonance imaging in patients with a hepatocellular carcinoma with or without other liver disease, excluding liver cirrhosis. *Sources: (Fischer, 2015; Lin, 2016)*

Very low GRADE	There is a very low certainty in the reported specificity of magnetic resonance imaging in patients with a hepatocellular carcinoma with or without other liver disease, excluding liver cirrhosis. *Sources: (Fischer, 2015; Lin, 2016)*

Very low GRADE	There is a very low certainty in the reported positive predictive value of magnetic resonance imaging in patients with a hepatocellular carcinoma with or without other liver disease, excluding liver cirrhosis. *Sources: (Fischer, 2015; Lin, 2016)*

Very low GRADE	There is a very low certainty in the reported negative predictive value of magnetic resonance imaging in patients with a hepatocellular carcinoma with or without other liver disease, excluding liver cirrhosis. *Sources: (Fischer, 2015; Lin, 2016)*

Overwegingen – van bewijs naar aanbeveling

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

Er werden drie primaire studies geselecteerd in de literatuuranalyse over de diagnostische accuratesse van CT en/of MRI voor het detecteren van hepatocellulaire carcinomen bij patiënten met of zonder achterliggende leverziekten in een niet cirrotische lever (Kim, 2011; Fischer, 2015; Lin, 2016).

Er was een redelijk tot zeer laag vertrouwen in de accuratesse parameters van CT-scans vanwege een risico op bias in de primaire studies(zoals beoordeeld door Nadarevic (2021) en (2022)) en de imprecisie. De imprecisie varieert tussen analyses en er is oplopend meer vertrouwen in de gerapporteerde accuratesse schatters van CT-scans naarmate de groepen in de analyses groter worden en hiermee de precisie van de accuratesse schatter toeneemt. Kleinere groepen in de analyses zijn bijvoorbeeld patiënten met een 1-2cm HCC (ten opzichte van >2cm) en groepen patiënten met een F0 of F0-1 METAVIR score (ten opzichte van F0-3) (Lin, 2016), waar er minder vertrouwen bestaat in de gerapporteerde accuratesse schatters door meer imprecisie. Naarmate er minder deelnemers in de sub-analyses zaten nam het vertrouwen af tot (zeer) laag. Hetzelfde patroon is zichtbaar voor de positief en negatief voorspellende waarde (Lin, 2016). Doordat er minder patiënten met kleinere hepatocellulair carcinomen (dat wil zeggen 1 tot 2 centimeter) dan met grotere hepatocellulaire carcinomen (dat wil zeggen >2 centimeter) in de steekproef van Lin (2016) zitten, zijn de accuratesseschatters in de sub-analyses voor kleinere hepatocellulair carcinomen minder precies dan die voor de grotere carcinomen. Kim (2011) deelde de steekproef met laesies groter dan twee centimeter, maar zonder levercirrose, op in een hoog-risico groep (sensitiviteit: 0,82 (95%BHI: 0,67 tot 0,91), specificiteit: 0,92 (95%BHI: 0,62 tot 0,99)) en een laag-risico groep (sensitiviteit: 0,87 (95%BHI: 0,60 tot 0,98), specificiteit: 0,90 (95%BHI: 0,68 tot 0,98)).

Voor beeldvorming met MR was er een zeer laag vertrouwen in de accuratesse parameters door risico op vertekening en imprecisie. Fischer (2015) vond vier MR beeldkenmerken die geassocieerd waren met hepatocellulair carcinomen bij patiënten zonder levercirrose en rapporteerde de diagnostische accuratesse: *hypointens op T1* (sensitiviteit: 0,78 (95%BHI: 0,65 tot 0,88), specificiteit: 0.63 (95%CI: 0.49 tot 0.64)), *niet isointens op T2* (sensitiviteit: 0,85 (95%BHI: 0,73 tot 0,94)), *geen centrale aankleuring* (sensitiviteit: 0,69 (95%BHI: 0,55 tot 0,81), specificiteit: 0,73 (95%BHI: 0,59 tot 0,84)), en de *aanwezigheid van satelliet laesies* (sensitiviteit: 0,24 (95%BHI: 0,13 tot 0,37), specificiteit: 0,96 (95%BHI: 0,87 tot 1,00)). Wanneer twee van de vier kenmerken positief zijn was de sensitiviteit 0,98 en de specificiteit 0,75. De 95% betrouwbaarheidsintervallen werden hier niet bij gerapporteerd en konden niet worden berekend. Lin (2016) gaf ook de accuratesse weer van MRI. Net als bij de accuratesse van CT-scans was imprecisie aanwezig in meer of mindere mate en afhankelijk van de sub-analyses. Schattingen waren preciezer voor grotere hepatocellulair carcinomen (>2 centimeter) dan voor kleinere (1 tot 2 centimeter). Een soortgelijk patroon is te zien wanneer de groepen groter worden bij sub-analyses op basis van de METAVIR score, waarbij de geanalyseerde groep stapsgewijs werd uitgebreid met een hogere mate van fibrotisering (dat wil zeggen F0, F0-1, F0-2, F0-F3). Hoe meer imprecisie er aanwezig is, hoe onzekerder men is over de accuratesseschatter.

Samenvattend is de accuratesse de diagnose van HCC op beeldvorming (CT of MRI) redelijk, maar onvoldoende om bij niet-cirrotische levers af te zien van een tumorbiopsie.

<u>Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)</u>
Het belangrijkste doel van het verrichten van een tumorbiopsie is meer zekerheid te krijgen over de diagnose.

De belangrijkste voordelen van een biopt voor de patiënt zijn 1) zekerheid over de diagnose; 2) meer duidelijkheid omtrent de prognose; 3) ten behoeve van de verdere behandeling, onder andere biopt wenselijk respectievelijk vereist bij systeemtherapie en transplantatie bij non-cirrose. De belangrijkste nadelen van een biopt voor de patiënt zijn 1) het betreft een belastende interventie (punctie met dagopname); 2) er is een risico op complicaties 3) er is een risico dat de biopsie geen diagnose oplevert. Het kan ook blijken dat de punctie niet mogelijk is.

De waarden en voorkeuren van de patiënt dienen te worden besproken. Het is een individuele afweging of de patiënt de nadelen van het biopt tegen de voordelen vindt opwegen. Indien een biopt geen verdere consequenties heeft voor de behandeling kan hiervan in overleg met de patiënt worden afgezien.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>
De indicatie voor een tumorbiopt bij patiënten met niet-cirrotische levers blijft staan en conform eerdere richtlijnen is alléén beeldvorming niet voldoende. Deze overweging kan per patiënt in het multidisciplinair overleg (MDO) worden besproken en gewogen.

Het verrichten van een biopt bij een verdenking op een HCC in een niet-cirrotische lever is aanvaardbaar en conform de huidige klinische praktijk.

Het verdient de voorkeur om de diagnostiek bij een verdenking op een HCC in een niet-cirrotische lever in samenspraak met gespecialiseerde centra te verrichten. Dit is van belang gezien de relatief lage incidentie van levertumoren, kennis en ervaring met eventuele onderliggende leverziekten, de benodigde ervaring in de beoordeling van beeldvorming, en

ook in het licht van histopathologisch onderzoek met mogelijk gespecialiseerd aanvullend moleculair onderzoek en immuunhistochemische kleuringen.

Bij de diagnose van een HCC dient het maken van een behandelplan te gebeuren in het MDO van een tertiair verwijscentrum in HCC, om de kwaliteit en uniformiteit in de diagnose en behandeling te waarborgen.

Aanbevelingen

Aanbeveling-1

Rationale van de aanbeveling

Er is onvoldoende zekerheid dat alléén beeldvorming voldoende is voor een accurate diagnostiek van een HCC bij patiënten zonder levercirrose. Voor het vaststellen van een hepatocellulair carcinoom in een niet-cirrotische lever wordt een biopsie aanbevolen. Door de lage incidentie van HCC bij patiënten zonder levercirrose, kennis en ervaring met eventueel onderliggende leverziekten, de benodigde ervaring met het beoordelen van beeldvorming en de mogelijkheid voor gespecialiseerde pathologische onderzoeken heeft het de voorkeur om de diagnostiek bij verdenking op HCC van patiënten zonder levercirrose in samenspraak met gespecialiseerde centra te verrichten.

Verricht een tumorbiopt bij patiënten met een verdenking op een HCC in een niet-cirrotische lever, gezien alléén beeldvorming niet voldoende is.

Bespreek de beeldvorming en besluitvorming omtrent tumorbiopsie in een MDO (zie SONCOS 2023).

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Bijlagen bij module 9

Kennislacunes

What is the diagnostic accuracy of MRI or a multiphasic CT-scan in patients suspected of a hepatocellular carcinoma with or without liver disease, but excluding liver cirrhosis, compared to histology as a reference standard?

Geldigheid en Onderhoud

Module[3]	Regiehouder(s)[4]	Jaar van autorisatie	Eerstvolgende beoordeling actualiteit richtlijn[5]	Frequentie van beoordeling op actualiteit[6]	Wie houdt er toezicht op actualiteit[7]	Relevante factoren voor wijzigingen in aanbeveling[8]

Implementatieplan

Aanbeveling	Tijdspad voor implementatie: <1 jaar, 1-3 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
1e							
2e							
etc							

[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, et cetera.

[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.

[3] Naam van de module

[4] Regiehouder van de module (deze kan verschillen per module en kan ook verdeeld zijn over meerdere regiehouders)

[5] Maximaal na vijf jaar

[6] (half)Jaarlijks, eens in twee jaar, eens in vijf jaar

[7] regievoerende vereniging, gedeelde regievoerende verenigingen, of (multidisciplinaire) werkgroep die in stand blijft

[8] Lopend onderzoek, wijzigingen in vergoeding/organisatie, beschikbaarheid nieuwe middelen

Evidence tables

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Kim 2011	Type of study[9]: Prospective cohort Setting and country: Hospital, Korea Funding and conflicts of interest: authors declare no competing interests, funding by a grant from Korea healthcare Technology R&D project (Grant #A084826, Ministry of health welfare and family affairs)	Inclusion criteria: Patients with hepatic masses >2cm, admitted to the hepatology department of Asan Medical Center (Korea) between December 2006 and June 2009. Exclusion criteria: Received CT as staging work-up for a known primary extrahepatic malignancy, terminal stage of the disease, severe coagulopathy, intraperitoneal bleeding from spontaneously ruptured tumors. N= 62 (group 2) N= 37 (group 3)	Describe index test: Helical CT with 4 phases (precontrast, arterial, portal, delayed). Slice thickness was 5mm and table feed was 5mm. Iopromide was used as a nonionic contrast agent (120ml, 3.5ml/sec via power injector). Scanning delay was determined using SmartPrep. Arterial phase, portal phase and delayed phase scanning began at 24, 72-90 and 180sec after descending aortic enhancement reached a threshold of 100HU above precontrast attenuation. CT findings were read by two radiologists (10 and 20 years experience in liver imaging) Cut-off point(s): Hypervascular enhancement pattern in the arterial phase and washout in the portal/delayed phase were classified as typically vascular. Tumors showing mixed	Describe reference test[11]: Fine Needle Biopsy under ultrasound guidance. At least two cores of liver tissue were obtained from each patient and stained with haematoxylin-eosin. If a conclusive result was not obtained, a second FNB was recommended. Cut-off point(s): International Working Party criteria.	Time between the index test en reference test: Unclear For how many participants were no complete outcome data available? 11 patients refused a second FNB and were excluded from analysis Reasons for incomplete outcome data described? Refusal of second FNB	Outcome measures and effect size (include 95%CI and p-value if available)[4]: <u>Group 2 CT detecting HCC >2cm:</u> Sens: 81.6% (95%CI: 0.67-0.91) Spec: 92.3% (95%CI: 0.62-0.99) PPV: 97.6% (95%CI: 0.86-0.99) NPV: 57.1% (95%CI: 0.34-0.77) <u>Group 3 CT detecting HCC >2cm:</u>	Patients with AFP>200ng/ml or typical enhancement patten on dynamic CT and with risk factors for HCC and were candidates for surgical resection did not undergo fine needle biopsy. Patients with inconclusive FNB results were excluded from analysis. Group 2 = high risk patient without cirrhosis (non-cirrhotic patient positive for hepatitis B surface antigen or anti-HCV) Group 3 = low risk patient without

[9] 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)

[11] 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).

		Prevalence: Group 2: 49/62=79% Group 3: 16/37=43.2% Mean age ± SD: Group 2: 52 (30-71) Group 3: 55 (21-81) Sex: % M / % F Group 2: 84%/16% Group 3: 57%/43% Other important characteristics: Hepatitis B: Group 2: 56 Group 3: - Hepatitis C: Group 2: 5 Group 3: - Hepatitis B and C: Group 2: 1 Group 3: -	areas of hyper and hypovascularity (with >70% hypervascular area) were considered a typical enhancement pattern. Other patterns were considered atypical. Comparator test[10]: - Cut-off point(s): -			Sens: 87.5% (95%CI: 0.60-0.98) Spec: 90.5% (95%CI: 0.68-0.98) PPV: 87.5% (95%CI: 0.60-0.98) NPV: 90.4% (95%CI: 0.68-0.98)	cirrhosis (non-cirrhotic patient negative for hepatitis B surface antigen and anti-HCV)
Lin 2016	Type of study: Retrospective	Inclusion criteria: Patients that underwent tumor resection or liver	Describe index test: CT: helical CT with 4-phases (non-contrast, arterial, portal, delayed) aquired in a clockwise direction in	Describe reference test: Histological and surgical reports	Time between the index test en reference test:	Outcome measures and effect size (include 95%CI	Two subsamples: resection and liver transplantation. Patients without a

[10] Comparator test is vergelijkbaar met de C uit de PICO van een interventievraag. Er kunnen ook meerdere tests worden vergeleken. Voeg die toe als comparator test 2 etc. Let op: de comparator test kan nooit de referentiestandaard zijn.

	Setting and country: Hospital, Taiwan Funding and conflicts of interest: no specific funding received, authors declared that there were no conflicts of interest	transplantation in Chang Gang Memorial Hospital between January 2006 and October 2010 Exclusion criteria: No liver CT or MRI before surgery, no pathological fibrosis score available, no tumor in the explanted liver. N=841 total Prevalence: CT: 100% Mean age ± SD: CT: 55.81 (12.27) MRI: 54 (12.49) Sex: M / F CT: 555/201 MRI: 142/62 Other important characteristics: Mean tumor size (cm): CT: 5.44 (SD 4.12) MRI: 4.04 (SD 3.13) Fibrosis level CT:	5mm sections. Contrast medium was used (2ml/sec, 80ml total). Thirty second after injection the scan for the arterial phase started. Portal phase scan started 20 sec after the arterial phase and the venous phase started 20 sec after the portal phase. MRI: 1.5-2T MRI including contrast medium (intravenous Gd-DTPA, 0.2mg/kg ar 1.6-1.8 ml/sec). pulse sequences were T1WI / T2WI / T2WI Fsat / heavy T2WI, long T2WI, enhancedT1WI in three phases. First phase was obtained 15 sec after contrast infusion, and the second and third phase after 30 sec intervals. Eight mm thickes and 2mm gap were used for the sequences. Cut-off point(s): Early enhancement in arterial phase AND early washout in venous phase Comparator test: - Cut-off point(s): -	Cut-off point(s): -	Not specified For how many participants were no complete outcome data available? NA, retrospective Reasons for incomplete outcome data described? -	and p-value if available): <u>CT detecting 1-2cm tumours in F0 group:</u> Sens: 5/7 (71.4%) Spec: 1/1 (100%) PPV: 5/5 (100%) NPV: 1/3 (33.3%) <u>CT detecting 1-2 tumours in F0-1 group:</u> Sens: 11/18 (61.1%) Spec: 1/2 (50%) PPV: 11/12 (91.7%) NPV: 1/8 (12.5%) <u>CT detecting 1-2cm tumours in F0-2 group:</u> Sens: 14/21 (66.7%) Spec: 1/3 (33.3%) PPV: 14/16 (87.5%) NPV: 1/8 (12.5%) <u>CT detecting 1-2cm tumours in F0-3 (non-cirrhotic) group:</u> Sens: 30/38 (78.9%)	tumor in the explanted liver were excluded. N=841 patients recruited, n=756 CT and n=204 MRI. Thus some patients received both a CT and MRI, while others received a single CT or MRI. n=756 CT of which n= 131 had a tumor 1-2cm and n=625 had >2cm. 131+625=756, thus seems like 100% prevalence of HCC from table 1.

		F0: n=104 F1: n=88 F2: n=40 F3: n=77 F4= 281 Fibrosis level MRI: F0: n=21 F1: n=18 F2: n=2 F3: n=14 F4=90 Non hepatitis B or C: CT: 202 MRI: 65 Hepatitis B: CT: 374 MRI: 96 Hepatitis C: CT: 157 MRI: 36 Hepatitis B and C: CT: 22 MRI 6				Spec: 18/23 (78.3%) PPV: 30/35 (85.7%) NPV: 18/26 (69.2%) <u>CT detecting >2cm tumours in F0 group:</u> Sens: 74/85 (87.1%) Spec: 10/11 (90.9%) PPV: 74/75 (98.7%) NPV: 13/34 (38.2%) <u>CT detecting >2 tumours in F0-1 group:</u> Sens: 135/156 (86.5%) Spec: 13/16 (81.3%) PPV: 135/138 (97.8%) NPV: 13/34 (38.2%) <u>CT detecting >2cm tumours in F0-2 group:</u> Sens: 166/192 (86.5%)	

						Spec: 13/16 (81.3%) PPV: 166/169 (98.2%) NPV: 13/39 (33.3%) <u>CT detecting >2cm tumours in F0-3 (non-cirrhotic) group:</u> Sens: 239/274 (87.2%) Spec: 107/135 (79.3%) PPV: 239/267 (89.5%) NPV: 107/142 (75.4%) <u>MRI detecting 1-2cm tumours in F0 group:</u> Sens: 1/1 (100%) Spec: 1/1 (100%) PPV: 1/1 (100%) NPV: 1/1 (100%) <u>MRI detecting 1-2 tumours in F0-1 group:</u> Sens: 2/3 (66.7%) Spec: 1/1 (100%) PPV: 2/2 (100%) NPV: 1/2 (50%)	

						<u>MRI detecting 1-2cm tumours in F0-2 group:</u> Sens: 2/3 (66.7%) Spec: 1/1 (100%) PPV: 2/2 (100%) NPV: 1/2 (50%) <u>MRI detecting 1-2cm tumours in F0-3 (non-cirrhotic) group:</u> Sens: 5/6 (83.3%) Spec: 8/10 (80%) PPV: 5/7 (71.4%) NPV: 8/9 (88.9%) <u>MRI detecting >2cm tumours in F0 group:</u> Sens: 10/14 (71.4%) Spec: 4/5 (80%) PPV: 10/11 (90.9%) NPV: 4/8 (50%) <u>MRI detecting >2 tumours in F0-1 group:</u> Sens: 21/28 (75%) Spec: 5/7 (71.4%) PPV: 21/23 (91.3%) NPV: 5/12 (41.7%)	

						<u>MRI detecting >2cm tumours in F0-2 group:</u> Sens: 23/30 (76.7%) Spec: 5/7 (71.4%) PPV: 23/25 (92%) NPV: 5/12 (41.7%) <u>MRI detecting >2cm tumours in F0-3 (non-cirrhotic) group:</u> Sens: 34/43 (79.1%) Spec: 43/53 (81.1%) PPV: 34/44 (77.3%) NPV: 43/53 (82.7%)	
Fischer 2015	Type of study: Retrospective from trial (consecutive recruitment) Setting and country: Multicenter, hospital Funding and conflicts of interest: Authors declare that there are no CoIs	Inclusion criteria: MRI prior to surgery for a suspicious HHC lesion, histopathologic evidence forr HCC, histopathologic evidence of a non-cirrhotic liver, and time between MRI and surgery <2 months Exclusion criteria: not reported	Describe index test: Three protocols were used: - Single contrast liver with extracellular fluid agent (n=53) - Single contrast liver with hepatobiliary-specific agent (n=42) - Double contrast with ECF and reticuloendothelial-specific agents (n=12) Five centres used different sequences in the coronal and/or axial plane: - T1 Dyn lava	Describe reference test: Histopathological examination of surgical specimen by macroscopic analysis and tissue sampling (both tumoral and non-tumoral liver). Immunihistochemistry was performed for final diagnosis Cut-off point(s): NR	Time between the index test and reference test: <2 months between imaging and surgery For how many participants were no complete outcome data available?	Outcome measures and effect size (include 95%CI and p-value if available): Multiple regression identified 4 factors associated with HHC: T1-intensity (hypointense)	

		N=107 Prevalence: 51.4% Median age ± (IQR): Benign: 34 (28-45) HCC: 61 (45-71) Sex, n, M/F: Benign: 10/42 HCC: 36/19 HBV status, -/+/unknown: Benign: 43/1/8 HCC: 40/11/4 HCV status, -/+/unknown: Benign: 44/0/8 HCC: 47/4/4 Median AFP (IQR): Benign: 2.3 (1.5-4.0) HCC: 3.5 (2.7-7.4) Other important characteristics:	- T1 flash FS - T1 flash in/opp - T1 in/opp - T1 vibe 3D dyn - T2 blade (TSE) - T2 FRFSE - T2 FS RT - T2 SSFSE - T2 SSFSH - T2 trufi - T2 TSE - T2Haste - T2Haste fat sat Time of repetition ranged from 3.3 to 9474. Time of echo ranged from 1.3 to 105. Flip angle ranged from 15 to 180. Slice thickness ranged from 3 to 10mm. Cut-off point(s): LI-RADS criteria at arterial, porto-venous, late, and hepatobiliary phase: - Lesion diameter - Lesion demarcation - Prescence of satellite lesions, central scar, haemorrhage, capsule appearance, presence of hepatic/portal vein infiltration - Signal intensity on unenhanced T1 and T2 - Relative signal intensity of in-phase versus. out-of-phase or		All 107 patients were used in the analysis Reasons for incomplete outcome data described? NA	(OR=4.81, 95%CI: 0.52-9.13) T2-intensity (not isointense) (OR= 5.07, 95%CI: 0.55-8.85) Central enhancement (no) (OR=3.31, 95%CI: 0.50-5.69) Satellite lesions (yes) (OR=5.78, 95%CI: 0.97-9.34) T1-intensity (hypointense) Sens: 0.78 (95%CI: 0.65-0.88)* Spec: 0.63 (95%CI: 0.49-0.64)* NPV: 0.73 (95%CI: 0.59-0.87) PPV: 0.69 (95%CI: 0.57-0.81) *95%Cis calculated with Revman 5 T2-intensity (not isointense) Sens: 0.85 (95%CI: 0.73-0.94)*	

			fat suppressed versus. non-fat-suppressed on unenhanced T1 or T2, precense of signal intensity homogeneity on unenhanced T1 or T2 - Signal intensity on contrast enhanced T1 compared to surrounding liver parenchyma			Spec: 0.50 (95%CI: 0.36-0.64)* NPV: 0.76 (95%CI: 0.60-0.92) PPV: 0.64 (95%CI: 0.52-0.76) *95%Cis calculated with Revman 5 Central enhancement (no) Sens: 0.69 (95%CI: 0.55-0.81)* Spec: 0.73 (95%CI: 0.59-0.84)* NPV: 0.69 (95%CI: 0.55-0.82) PPV: 0.73 (95%CI: 0.60-0.86) *95%Cis calculated with Revman 5 Satellite lesions (yes) Sens: 0.24 (95%CI: 0.13-0.37)* Spec: 0.96 (95%CI: 0.87-1.00)*	

						NPV: 0.54 (95%CI: 0.43-0.65) PPV: 0.87 (95%CI: 0.66-1.00) *95%Cis calculated with Revman 5 When any 2 of the 4 imaging features were positive, the sensitivity was 0.91 and the specificity was 0.75 for contrast enhanced MR (AUC=0.85, 95%CI: 0.77-0.93) All 4 features positive: specificity was 98% (sens not reported)	

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

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Kim 2011 (*RoB judgements from Nadarevic 2021)	Was a consecutive or random sample of patients enrolled? Yes* Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No*	Were the index test results interpreted without knowledge of the results of the reference standard? Yes* If a threshold was used, was it pre-specified? Yes*	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? No*	Was there an appropriate interval between index test(s) and reference standard? Unclear* Did all patients receive a reference standard? Unclear (n=24 received surgery instead of FNB, unclear whether a pathological assessment was included) Did patients receive the same reference standard? Unclear, n=24 did not receive FNB. Were all patients included in the analysis? No (n=11 refused a second FNB and were excluded from the analyses)	Are there concerns that the included patients do not match the review question? Yes* 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: HIGH***	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW***	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**	
Lin 2016 (*RoB judgements	Was a consecutive or random sample of patients enrolled? Yes*	Were the index test results interpreted without knowledge	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?	Are there concerns that the included patients do not match the review question?

from Nadarevic 2022)	Was a case-control design avoided? Unclear Did the study avoid inappropriate exclusions? No*	of the results of the reference standard? Yes* If a threshold was used, was it pre-specified? Yes*	Yes* Were the reference standard results interpreted without knowledge of the results of the index test? Yes*	Unclear* Did all patients receive a reference standard? Unclear Did patients receive the same reference standard? No* Were all patients included in the analysis? Yes*	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*
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: HIGH***	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW***	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW***	CONCLUSION Could the patient flow have introduced bias? **RISK: HIGH***	
Fischer 2015	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? Yes If a threshold was used, was it pre-specified? Yes	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	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? Yes Were all patients included in the analysis? Yes	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

	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: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: LOW**	

Table of excluded studies

From the included studies by Nadarevic (2021; 2022)

Author and year	Reason for exclusion
Hsiao 2019	No subanalyses for patients without cirrhosis
Serste 2012	No subanalyses for patients without cirrhosis
Besa 2017	No subanalyses for patients without cirrhosis
Brunsing 2019	No subanalyses for patients without cirrhosis
Dumitrescu 2013	No subanalyses for patients without cirrhosis
Marks 2015	No subanalyses for patients without cirrhosis
Min 2018a	No subanalyses for patients without cirrhosis
Serste 2012	No subanalyses for patients without cirrhosis
Teefey 2003	No subanalyses for patients without cirrhosis
Vietti Violi 2020	No subanalyses for patients without cirrhosis

From the excluded by Nadarevic (2021, 2022)

Author and year	Reason for exclusion
Abdelfattah, M. R. and Al-Mana, H. and Neimatallah, M. and Elsiesy, H. and Al-Sebayel, M. and Broering, D. C., (2013), Usefulness of combination of imaging modalities in the diagnosis of hepatocellular carcinoma using Sonazoid(R)-enhanced ultrasound, gadolinium diethylene-triamine-pentaacetic acid-enhanced magnetic resonance imaging, and contrast-enhanced computed tomography	Poster presentation
Akhtar, S. and Hussain, M. and Ali, S. and Maqsood, S. and Akram, S. and Abbas, N., (2020), Hepatocellular carcinoma lesion characterization: single-institution clinical performance review of multiphase gadolinium-enhanced MR imaging--comparison to prior same-center results after MR systems improvements	Unclear whether there were patients with(out) cirrhosis and how largre the propotion then was
Alaboudy, A. and Inoue, T. and Hatanaka, K. and Chung, H. and Hyodo, T. and Kumano, S. and Murakami, T. and Moustafa, E. F. and Kudo, M., (2011), Multiparametric Gd-EOB-DTPA magnetic resonance in diagnosis of HCC: dynamic study, hepatobiliary phase, and diffusion-weighted imaging compared to histology after orthotopic liver transplantation	At least 2 representative cases had cirrhosis, no apparent subanalyses for non-cirrhosis sub sample (if there were any)
Becker-Weidman, D. J. and Kalb, B. and Sharma, P. and Kitajima, H. D. and Lurie, C. R. and Chen, Z. and Spivey, J. R. and Knechtle, S. J. and Hanish, S. I. and Adsay, N. V. and Farris, A. B., 3rd and Martin, D. R., (2011), Focal liver lesions: detection and characterization at double-contrast liver MR Imaging with ferucarbotran and gadobutrol versus single-contrast liver MR imaging	Unclear whether there were patients with(out) cirrhosis and how largre the propotion then was
Faletti, R. and Cassinis, M. C. and Fonio, P. and Bergamasco, L. and Pavan, L. J. and Rapellino, A. and David, E. and Gandini, G., (2015), Detection of hypervascular hepatocellular carcinoma: comparison of SPIO-enhanced MRI with dynamic helical CT	Cirrhosis etiology was described for all n=28 participants
Heilmaier, C. and Lutz, A. M. and Bolog, N. and Weishaupt, D. and Seifert, B. and Willmann, J. K., (2009), (Differential diagnosis of focal liver lesions using contrast-enhanced MRI with SHU 555 A in comparison with unenhanced MRI and multidetector spiral-CT)	Cirrhosis was confirmed in all patients
Hori, M. and Murakami, T. and Kim, T. and Tsuda, K. and Takahashi, S. and Okada, A. and Takamura, M. and Nakamura, H., (2002), Diagnostic validity for sequential approach of dynamic image modalities in high-risk patients for hepatocellular carcinoma	23/41 patients had hepatic cirrhosis, no subanalysis for non-cirrhotic
Jung, G. and Poll, L. and Cohnen, M. and Saleh, A. and Vogler, H. and Wettstein, M. and Willers, R. and Modder, U. and Koch, J. A., (2005), The capsule appearance of hepatocellular carcinoma in gadoxetic acid-enhanced MR imaging: Correlation with pathology and dynamic CT	Article in german
Kang, H. T. and Shin, H. D. and Kim, S. B. and Song, I. H., (2012), Using low tube voltage (80kVp) quadruple phase liver CT for the detection of hepatocellular carcinoma: two-year experience and comparison with Gd-EOB-DTPA enhanced liver MRI	Poster presentation
Kim, B. and Lee, J. H. and Kim, J. K. and Kim, H. J. and Kim, Y. B. and Lee, D., (2018), Gd-EOB-DTPA dynamic contrast-enhanced magnetic resonance imaging is more effective than enhanced 64-slice CT for the detection of small lesions in patients with hepatocellular carcinoma	All patients had an underlying cause of cirrhosis described

Lee, C. H. and Kim, K. A. and Lee, J. and Park, Y. S. and Choi, J. W. and Park, C. M., (2012), Diagnostic sensitivity of hepatocellular carcinoma imaging and its application to non-cirrhotic patients	Unclear whether there were patients with(out) cirrhosis and how largre the propotion then was
Li, J. and Li, X. and Weng, J. and Lei, L. and Gong, J. and Wang, J. and Li, Z. and Zhang, L. and He, S., (2018), Hepatocellular carcinoma in patients undergoing living-donor liver transplantation. Accuracy of multidetector computed tomography by viewing images on digital monitors	Unclear whether there were patients with(out) cirrhosis and how largre the propotion then was
Lin, M. T. and Chen, C. L. and Wang, C. C. and Cheng, Y. F. and Eng, H. L. and Wang, J. H. and Chiu, K. W. and Lee, C. M. and Hu, T. H., (2011), Focal liver disease: comparison of dynamic contrast-enhanced CT and T2-weighted fat-suppressed, FLASH, and dynamic gadolinium-enhanced MR imaging at 1.5 T	Seems to contain duplicate data with Lin 2016
Maetani, Y. S. and Ueda, M. and Haga, H. and Isoda, H. and Takada, Y. and Arizono, S. and Hirokawa, Y. and Shimada, K. and Shibata, T. and Kaori, T., (2008), MRI texture analysis for differentiation of malignant and benign hepatocellular tumors in the non-cirrhotic liver	All n=41 patients had liver cirrhosis (underlying etiology described for all 41 patients)
Semelka, R. C. and Shoenut, J. P. and Kroeker, M. A. and Greenberg, H. M. and Simm, F. C. and Minuk, G. Y. and Kroeker, R. M. and Micflikier, A. B., (1992), Low specificity of washout to diagnose hepatocellular carcinoma in nodules showing arterial hyperenhancement in patients with Budd-Chiari syndrome	n=4 patients with hepatocellular cancer (of n=71) and all 4 had cirrhosis
Stocker, D. and Marquez, H. P. and Wagner, M. W. and Raptis, D. A. and Clavien, P. A. and Boss, A. and Fischer, M. A. and Wurnig, M. C., (2018),	Unclear diagnostic criteria (not specific)
Van Wettere, M. and Purcell, Y. and Bruno, O. and Payance, A. and Plessier, A. and Rautou, P. E. and Cazals-Hatem, D. and Valla, D. and Vilgrain, V. and Ronot, M., (2019),	mixed reference standards: histopatholoy on resection or biopsy, or clinical and biological follow-up of 12 months

Literature search strategy

Algemene informatie

Richtlijn: NVMDL hepatocellulair carcinoom	
Uitgangsvraag: UV 10 Is diagnostiek middels MRI of CT beter dan diagnostiek middels histologie bij patiënten met levertumor verdacht voor hepatocellulair carcinoom zonder bekende levercirrose?	
Database(s): Ovid/Medline, Embase	Datum: 21-7-2022
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: HCC EN (MRI of CT) EN histologie EN sensitivity, specificity Vanwege de hoge aantallen worden eerst de systematische reviews aangeboden. Eventueel kan worden overwogen om AI in te zetten, of bij het vinden van een relevante SR, het resultaat aanvullen met recente observationele studies.	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 21-7-2022 met relevante zoektermen gezocht naar systematische reviews over diagnostiek middels MRI of CT versus histologie bij patiënten met levertumor verdacht voor hepatocellulair carcinoom. De literatuurzoekactie leverde 33 unieke treffers op.	

5 Zoekopbrengst

	EMBASE	OVID/MEDLINE	Ontdubbeld
SRs	26	17	33
RCTs			
Observationele studies			
Overig			
Totaal			

Zoekstrategie

Embase

No.	Query	Results
#18	#15 NOT #14 NOT #13	764
#17	#14 NOT #13	22
#16	#13 OR #14 OR #15	785
#15	(#9 OR #10) AND #12	943
#14	#8 AND #12	32
#13	#7 AND #12 SR	26
#12	#11 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)	1158
#11	#5 AND #6	1813
#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	12836329

	risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#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	'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	8425978
#5	#3 AND #4	7142
#4	'histology'/exp/mj OR 'histopathology'/exp/mj OR 'immunohistochemistry'/exp/mj OR 'antigen staining':ti,ab,kw	1668922

	OR 'immunohistochem*':ti,ab,kw OR 'immunostaining':ti,ab,kw OR 'immuno histochem*':ti,ab,kw OR 'histopatholog*':ti,ab,kw OR 'histolog*':ti,ab,kw	
#3	#1 AND #2	15678
#2	'nuclear magnetic resonance imaging'/exp OR ('magnetic resonance':ab,ti AND (image:ab,ti OR images:ab,ti OR imaging:ab,ti)) OR mri:ab,ti OR mris:ab,ti OR nmr:ab,ti OR mra:ab,ti OR mras:ab,ti OR zeugmatograph*:ab,ti OR 'mr tomography':ab,ti OR 'mr tomographies':ab,ti OR 'mr tomographic':ab,ti OR 'proton spin':ab,ti OR ((magneti*:ab,ti OR 'chemical shift':ab,ti) AND imaging:ab,ti) OR fmri:ab,ti OR fmris:ab,ti OR 'computer assisted tomography'/exp OR 'cat scan':ti,ab,kw OR ((compute* NEAR/3 tomograph*):ti,ab,kw) OR ct:ti,ab,kw	2616434
#1	'liver cell carcinoma'/exp/mj OR ('liver cancer'/de AND 'primary tumor'/de) OR (((hepat* OR liver) NEAR/3 carcinom*):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw OR ((primary NEAR/3 liver):ti,ab,kw)	215358

Ovid/Medline

#	Searches	Results
12	11 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) SR	17
11	9 and 10	17
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.	609461
9	7 and 8	1383
8	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/	7479530
7	5 and 6	3042

6	exp Histology/ or exp Immunohistochemistry/ or antigen staining.ti,ab,kf. or immunohistochem*.ti,ab,kf. or immunostaining.ti,ab,kf. or immuno histochem*.ti,ab,kf. or histopatholog*.ti,ab,kf. or histolog*.ti,ab,kf.	1637220
5	3 and 4	16918
4	Carcinoma, Hepatocellular/ or (hepat* adj3 carcinom*).ti,ab,kf. or hepatocarcinom*.ti,ab,kf. or hepatoma.ti,ab,kf. or (liver adj3 primary).ti,ab,kf.	166211
3	1 or 2	1555005
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.	803877
1	exp magnetic resonance imaging/ or ("magnetic resonance" and (image or images or imaging)).ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or "mr tomography".ti,ab,kf. or "mr tomographies".ti,ab,kf. or "mr tomographic".ti,ab,kf. or "proton spin".ti,ab,kf. or ((magneti* or "chemical shift") and imaging).ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf.	900727

Module 10 – minimaal invasieve chirurgie versus ablatie

Uitgangsvraag

Is minimaal invasieve chirurgie (robot of laparoscopie, MIC) te prefereren boven ablatie?

Inleiding

Laparoscopische of robot-geassisteerde leverresectie is een nieuwe benadering voor de behandeling van levertumoren en er is gesuggereerd dat dit voordelen biedt ten opzichte van open leverresectie, ook bij cirrotische patiënten. In de meeste studies is de laparoscopische en/of robot-geassisteerde (minimaal invasieve chirurgie (MIC)) leverresectie vergeleken met een open leverresectie bij patiënten met HCC zonder achtergrond cirrose of (goed) gecompenseerde cirrose. Deze studies laten zien dat de laparoscopische en/of robot-geassisteerde benaderingen haalbaar zijn, met vergelijkbare korte en lange-termijn resultaten als de open chirurgie. De vraag blijft echter of de laparoscopische en/of robot-geassisteerde benadering voordelen heeft in die gevallen waarbij percutane ablatie ook een optie is. Percutane ablatie wordt gezien als een procedure met minder morbiditeit, een korter ziekenhuisverblijf en minder kosten.

Bijgevolg blijft discussie bestaan over de voorkeursaanpak wanneer zowel MIC als percutane ablatie een geldige optie lijken; dat wil zeggen bij tumoren kleiner dan 3,0 cm diameter. Hiervoor is dit systematisch overzicht van de literatuur uitgevoerd.

For the international exchange of this literature review, the next part is written in English.

Search and select

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

> Is minimally invasive surgery (robot or laparoscopy) preferable to ablation (stratified by segment)?

P: hepatocellular carcinoma (HCC) patients with a tumor <3,0 cm, stratified by location (segments);
I: minimally invasive surgery (MIS, robotic or laparoscopic);
C: ablation;
O: Postoperative complications (clavien-dindo).

<u>Relevant outcome measures</u>

The guideline development group considered post-operative complications (Clavien-Dindo) as critical measurement for clinical decision making.

Post-operative complications were defined following Clavien Dino system of grading surgical Complications (Dindo, 2004). These can also include morbidity and mortality that occur within 30 days after an operation.

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

<u>Search and select (Methods)</u>

Initially the databases Embase and Ovid/Medline were searched on 4th April 2022 with relevant search terms for systematic reviews and RCTs on minimally invasive, robotic surgery or laparoscopy in hepatocellular carcinoma. The detailed search strategy is depicted under

the tab Methods. The systematic literature search yielded 179 unique 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.
- Articles written in English or Dutch.

Eleven studies were initially selected based on title and abstract screening. After reading the full texts, all 11 studies were excluded. Most of them reported data that the working group considered too old (>10 years ago) due to recent developments regarding ablation such as microwave ablation, better imaging, more CT-guided, et cetera. In the meantime, also surgery has developed, with increased preference for minimally invasive surgery, robotics, and better preoperative imaging. The search included a recent meta-analysis Yang (2021) which included the relevant comparison between MIS and ablation. However, as the other included interventions we outside the scope of this review, we excluded it.

An update of the search was performed to search for observational studies after the search date of a network meta-analysis by Yang (2021). The search strategy has also been expanded to include systematic reviews and randomized controlled trials published after 4th April 2022. The updated systematic literature search resulted in another 754 hits.

The results have been deduplicated from those found previously. Studies were selected based on the following criteria: Patients with hepatocellular carcinoma, tumor smaller than 2.5/3 cm, that are either treated by minimally invasive surgery (robotic or laparoscopic) or ablation after the year 2016, data about one of the outcomes of interest were reported. Observational studies were excluded when they did not perform a propensity score analysis or that allowed more than 2 tumors (multifocal tumors). Twenty studies were selected based on title and abstract screening and, of these studies, 15 were excluded (see the table with reasons for exclusion under the tab Methods). 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

There are no RCTs that compared the treatment of HCC (<3cm) with surgery/MIV versus ablation.

Description of studies

Cheng (2022) examined the short-term and long-term outcomes of laparoscopic liver resection (LLR) and radiofrequency ablation (RFA) for patients with small HCC. They included patients with small HCC (defined as Barcelona Clinic Liver Cancer (BCLC) stage 0 or A, size ≤3 cm, ≤3 nodules on contrast CT scan or MRI with no evidence of macrovascular invasion) from April 2005 to August 2020. The median follow-up period was 34 months. In general, liver resection was first considered in all cases. All LLR (n=99) and RFA (n=31) were performed by the same team of hepatobiliary surgeons and interventional radiologists respectively. A 1:3 propensity score matching was conducted to match patients in the LLR group and RFA group. Prognostic indicators, i.e., age, gender, tumor size, tumor number, Child's grading, albumin, bilirubin, platelet count, international normalized ratio, alpha-fetoprotein level and

presence of cirrhosis on imaging were chosen for propensity score calculation. All patients followed the same protocol of preoperative workup and investigations including blood tests to determine liver function and alpha fetoprotein (AFP) level, as well as radiological assessment using contrasts CT scan and/or MRI. Tumors located in segments 7 or 8 were defined as posterosuperior lesions.

Conticchio (2021) investigated short- and long-term outcomes in radiofrequency ablation (RFA) compared with laparoscopic liver resection (LLR). This multicenter retrospective study included 184 patients who were treated from January 2009 to January 2019 in hospitals in France, Spain, Switzerland, and Italy. Patients had to be Child-Pugh class A and B, older than 70 years with a single hepatocellular carcinoma with max. 3 cm diameter, without any evidence of major portal/hepatic vein branch invasion and extrahepatic disease. A 1:1 propensity score matching was conducted to decrease selection bias by building a matched group of patients to compare perioperative characteristics, short- and long-term outcomes in resection and ablation groups. After matching, 58 patients were treated with RFA and LLR, respectively.

Ding (2022) analyzed differences in operation trauma, postoperative recovery, complications, cost and oncological efficacy of the two therapies to provide support for patients and doctors in decision-making of HCC patients treated with robot-assisted hepatectomy (RH) and microwave ablation (MWA). The inclusion criteria were as follows: (a) a diagnosis of HCC with pathological confirmation; (b) Barcelona Clinic Liver Cancer stage 0-A; (c) no treatment history; and (d) more than 6 months of follow-up. The exclusion criteria were as follows: (a) combined MWA or RFA during RH; (b) palliative treatment; and (c) switching from RH to open surgery during the operation (these patients were counted as RH failure cases but were not included in the final analysis). A total of 401 eligible patients who received MWA (n = 240, 59.9%) or RH (n = 161, 40.1%) were enrolled in our study. A 1:1 propensity score matching was conducted to adjust baseline imbalances of preoperative clinical factors between the two groups.

Results

Outcome 1- Post-operative complications

Cheng (2022) reported no significant difference regarding short-term post-operative outcomes between the laparoscopic liver resection (LLR) and radiofrequency ablation (RFA) group. One patient out of 99 patients in LLR group had laparoscopic segment 5 segmentectomy performed and complicated with gallbladder perforation required emergency laparoscopic cholecystectomy. There were no major complications (Clavien-Dindo grade 3+) among the 31 patients treated with RFA. These results are not statistically significant (p=0.574).

In the study of Conticchio (2021), the postoperative course did not show any evidence in the percentages of complications between the RFA and the LLR group (19 and 36%, p=0.06), nor in the level of severity (Clavien-Dindo grades III–IV) (0 versus 9% p=0.06). In neither group, death (Clavien-Dindo grade V) occurred during hospital stay.

Ding (2022) found no significant difference between robot-assisted hepatectomy (RH) and microwave ablation (MWA) in total complications, minor complications or severe complications between the two groups in the matched cohort (n=122, respectively). The RH group had seven (4.3%) severe complications. Three patients (Clavien-Dindo grade IV) entered the ICU after surgery due to uncontrollable fluctuating blood pressure (2 patients) and massive blood loss (1 patient), and four patients (Clavien-Dindo grade III) had severe postoperative bleeding (2 patients), hemothorax (1 patient) or bile leakage (1 patient). The

MWA group had three cases (1.3%) of severe complications. All were Clavien-Dindo grade III: subcapsular hemorrhage (1 patient) and pneumothorax requiring chest tube insertion (2 patients).

Level of evidence of the literature
The evidence derived from observational studies starts at low GRADE. Each comparison can be downgraded due to one of the following reasons:

- Risk of bias: Limitations in study design or execution (Risk of bias table).
- Inconsistency: Unexplained statistical heterogeneity (results differ between studies).
- Indirectness: Evidence comes from other PICO.
- Imprecision: Confidence intervals of the overall (pooled) effect are wide, thresholds for clinical decision-making are crossed or event size is small.
- Publication bias: it is suspected that not all evidence has been published (yet).

Post-operative complications: The level of evidence was downgraded by one level because of inconsistency (the results are always measured in different ways).

Conclusions

Outcome 1- Post-operative complications

Very low GRADE	Severe complication (≥grade III) rates are comparable in both groups, which meant that both have (extremely) high safety. *Sources: (Cheng, 2022;* Conticchio, 2021; Ding, 2022)

Overwegingen – van bewijs naar aanbeveling

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

Er is een literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met minimaal invasieve chirurgie (MIC) in vergelijking met ablatie bij patiënten met hepatocellulair carcinoom (HCC) kleiner dan 3 cm diameter. De werkgroep is overeengekomen alleen resultaten op te nemen van studies die niet ouder zijn dan 10 jaar. Er werden 3 niet-gerandomiseerde studies geselecteerd en uitgewerkt (Cheng, 2022**;** Conticchio, 2021; Ding, 2022). Voor de cruciale uitkomstmaat postoperatieve complicaties konden de gevonden studies niet gepoold worden omdat de resultaten voortkomen uit verschillende studie types en de resultaten verschillend gerapporteerd zijn. Daarnaast waren de studiebevindingen soms moeilijk met elkaar te vergelijken omdat de controle interventies van elkaar verschilden (indirectness) en waren er meerdere studies met een relatief kleine populatie en mede hierdoor een grote spreiding van de puntschatter van de uitkomstmaat (imprecision), waardoor de kwaliteit van dit bewijs ook naar beneden werd bijgesteld. De overall bewijskracht voor de cruciale uitkomstmaat is zeer laag.

Concluderend laten de drie geïncludeerde studies aanwijzingen zien dat ernstige complicaties (≥ graad III) in beide groepen vergelijkbaar zijn, hetgeen betekent dat beide behandelopties veilig zijn. De oorzaken van complicaties in beide groepen waren echter verschillend. Complicaties in de MIC-groep werden voornamelijk veroorzaakt door algemene anesthesie of massale bloedtransfusie, terwijl in de ablatiegroep de oorzaak van complicaties voornamelijk te wijten was aan het punctieproces (Ding, 2022). De overall bewijskracht is onvoldoende om hier een eenduidige conclusie uit te trekken.

Leverfalen wordt als een belangrijke complicatie beschouwd als het een (direct) gevolg is van de ingreep. In de literatuursamenvatting werden echter geen studies meegenomen die

het effect van MIC op leverfalen rapporteerden in vergelijking met ablatie voor patiënten met een hepatocellulair carcinoom kleiner dan 3 cm.

Ondanks het minimaal invasieve karakter van MIC resulteerde het toch in grotere wonden dan percutane ablatie en moet het onder algehele anesthesie worden uitgevoerd, met als gevolg een langer verblijf in het ziekenhuis voor postoperatief herstel en pijnbestrijding (Cheng, 2022). Dezelfde studie toonde ook dat MIC en ablatie een vergelijkbare algehele overleving hadden (91.8% versus 79.2% na 5 jaar); terwijl de MIC-groep een significant betere ziektevrije overleving (49.0% versus 30.3% na 5 jaar) en lokaal recidiefvrije overleving (96.0% versus 63.7% na 5 jaar) had in vergelijking met de ablatie-groep.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

De effectiviteit van de twee behandelopties dient te worden afgewogen tegen de voor- en nadelen. Het nut van de respectievelijke interventie is immers niet voor iedere patiënt gelijk en hangt af van leeftijd, conditie, ligging van de tumor, co-morbiditeit en andere factoren. Daarnaast kunnen lokaal ook verschillen bestaan wat betreft ervaring en voorkeur ten aanzien van de verschillende technieken en benaderingen. Door goede voorlichting door de behandelaar over de verwachte voor- en nadelen kan in gesprek met de individuele patiënt een keuze gemaakt worden (samen beslissen).

De werkgroep is van mening dat het belangrijk is tenminste de volgende zaken goed met de patiënt te bespreken:
Een levertransplantatie kan na terugkeer van ziekte HCC die zich beperkt tot de lever onder bepaalde omstandigheden een optie zijn. De (relatieve) leeftijdsgrens voor een transplantatie van 70 jaar speelt echter een rol (zie Module Prognostische factoren). Verder is belangrijk de algemene cardiovasculaire belasting en de langere opnameduur van een chirurgisch ingreep de bespreken (Shin, 2021). Deze aspecten kunnen ertoe leiden dat met name oudere patiënten vaker kiezen voor minder belastende behandelingen.

Kosten (middelenbeslag)

Zowel de korte als de lange termijn uitkomsten kunnen invloed hebben op de kosten. Helaas is dit in de literatuur voor deze uitgangsvraag niet uitgezocht.

Ding (2022) bekeek de economische effecten van microwave ablatie (MWA) en Robot-geassisteerde leverresectie en vond een groot kostenverschil tussen de twee groepen. In deze studie waren de totale medische kosten (berekening van de medische kosten en aanvullend materiaal) in de MWA-groep de helft van die in de RH-groep.

Het is echter aannemelijk dat kosten van complicaties na een resectie (MIC) hoger zijn dan na ablatie. Een behandeling met minder ernstige complicaties en een kortere opnameduur (ablatie) zal daarom zeer waarschijnlijk kosten effectiever zijn.

Ook de maatschappelijke kosten moeten worden meegewogen omdat na een techniek met een sneller herstel (ablatie) de patiënt weer eerder mee kan doen in het arbeidsproces.

De werkgroep is van mening dat de kosteneffectiviteit van de verschillende behandelingen nog moet worden uitgezocht.

Aanvaardbaarheid, haalbaarheid en implementatie

- Beschikbaarheid van een multidisciplinair team (conform SONCOS 2023 norm) met HCC expertise: hepatoloog, oncoloog, chirurg, patholoog, interventie radioloog en nucleair geneeskundige.
- Behandeling bij voorkeur in een expertiesecentra met veel ervaring van beide technieken. Dit zorgt ervoor dat een patiënt die op papier voor beide interventies geschikt is, ook daadwerkelijk beide opties krijgt aangeboden.
- Doorverwijzen naar of vroegtijdig overleg met een levertransplantatiecentrum verdient nadrukkelijk de voorkeur. Dit om te voorkomen dat bij patiënten, voor wie de ultieme behandeling een levertransplantatie is, deze optie niet of pas in een te ver gevordend stadium overwogen wordt. Streven is dat hiermee voor elke patiënt in Nederland een gelijke toegang tot transplantatie beschikbaar is.

Aanbeveling

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

De literatuur laat vergelijkbare gunstige resultaten zien voor beide behandelmogelijkheden (MIC en ablatie). De werkgroep stelt op basis van expertise dat ablatie een gunstiger complicatieprofiel heeft met minder kosten.

- Bespreek de HCC-patiënt in een MDO, ingericht conform Soncos 2023.
- Er kan een voorkeur zijn van MIC in het geval van:
  - Ligging van de afwijking (bijvoorbeeld tegen vitale structuren, perifeer of ligging tegen centrale galwegen).
  - Afwezige portale hypertensie.
  - Afwezige cirrose.
  - Behouden (rest)leverfunctie.
  - Relatief jonge leeftijd.

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Bijlagen bij module 10

Kennislacunes

- Kosteneffectiviteit van de verschillende behandelingen
- Oncologisch (langetermijns) uitkomsten vergeleken voor de verschillend technieken.

Evidence tables

Research question: Is minimally invasive surgery (robot or laparoscopy) preferable to ablation (stratified by segment)?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Cheng, 2022	Type of study: single-center retrospective analysis Setting and country: China Funding and conflicts of interest: none	Inclusion criteria: All patients underwent radiofrequency ablation (RFA) or laparoscopic liver resection (LLR) for small HCC (defined as BCLC stage 0 or A, sized ≤3 cm, ≤3 nodules on contrast CT scan or MRI with no evidence of macrovascular invasion) from April 2005 to August 2020 were included. Exclusion criteria:	Describe intervention For LLR, a 12-mm camera trocar was inserted at the subumbilical region, and 4–5 trocars of diameter 5–12 mm were used by the surgeon and assistant. Ultrasonic shear device or Cavitron Ultrasonic Surgical Aspirator (CUSA) was used to conduct liver parenchymal transection. Pringle maneuvers were employed selectively. Anatomical liver resection was defined as removal of the whole hepatic segment or subsegments	Describe control RFA were performed percutaneously using the Cool-tipTM RF Ablation System (Medtronic, USA) under local anesthesia. The RFA electrode was inserted under non-contrast ultrasound or CT scan guidance, with an intended ablative margin of at least 1 cm. Drain was placed only when clinically indicated.	Length of follow-up: Median follow-up was 34 months (range, 1–175 months). Loss-to-follow-up: I: none C: none Incomplete outcome data: Not reported	Outcome measures and effect size (include 95%CI and p-value if available): All complications: I: 12.1% C: 6.5% (p= 0.374) Major (Clavien-Dindo grade 3 or above) complications, I: 1.0% C: 0.0% (p=0.574) The LLR group and RFA group had similar overall survival rate (91.8% versus. 79.2% at 5-year, P=0.060); while the LLR group had a significantly better disease-free survival rate (49.0%	In general, liver resection was first considered in all cases. All LLR and RFA were performed by the same team of hepatobiliary surgeons and interventional radiologists respectively. 1:3 propensity score matching was conducted to match patients in the LLR group and RFA group. Prognostic indicators, i.e., age, gender, tumor size, tumor number, Child's grading, albumin, bilirubin, platelet count, international normalized ratio, alpha-fetoprotein level and presence of cirrhosis on imaging were

		n.a. <u>N total at baseline</u>: Intervention: 99 Control: 69 <u>N total after matching</u>: I: 99 C: 31 <u>Important prognostic factors</u>[2]: *Age ± SD:* *I: 63.60 ±9.86* *C: 65.48±11.73* *Number of tumors (1):* *I: 97.0%* *C:90.3%* *Tumor size (cm)* *I: 2.31 ±1.93* *C: 1.14±0.70* *Sex:* *I: 82.8% M* *C: 71.0% M*	supplied by the tumor bearing tributaries.			versus. 30.3% at 5-year, P=0.002) and local recurrence-free rate (96.0% versus. 63.7% at 5-year, P<0.001) when compared with the RFA group.	chosen for propensity score calculation. The analysis was carried out on an intention-to-treat basis. This study showed that both procedures were safe and feasible. RFA had a shorter hospital stay, while LLR had a lower local recurrence rate and better disease-free survival rate. Nevertheless, the overall survival was comparable between the two groups.
Magistri, 2020	Type of study: retrospective cohort analysis	<u>Inclusion criteria</u>: All consecutive patients treated by robotic liver	<u>Describe intervention</u> The RLR included 16 wedge resections and 8 segmentectomies, performed with or without	<u>Describe control</u> All patients were placed under conscious sedation, and the procedure was carried out under	<u>Length of follow-up</u>: The median follow-up time was 29 months (range 11–38) in the RLR group and 22 months	Outcome measures and effect size (include 95%CI and p-value if available): All complications: I: 38%	<u>All HCC patients were discussed by multidisciplinary board.</u> RLRs were performed using the da Vinci Si

	Setting and country: Italy Funding and conflicts of interest: none	resection (RLR) or percutaneous ablation) PA between January 2014 and October 2019 for a newly diagnosed single HCC, less than 3 cm in size (very early/early stages according to Barcelona Clinic Liver Cancer (BCLC) on chronic liver disease or liver cirrhosis <u>Exclusion criteria</u>: Patients with exophytic lesions, tumors close the hepatic hilum or major hepatic veins, and nodules undetectable by US were excluded from this analysis. <u>N total at baseline</u>:	intermittent hilar clamping (Pringle maneuver was performed in three cases: total clamping interval of 32, 50, and 72 min, respectively) and using a combination of monopolar energy, bipolar energy, and da Vinci Harmonic ACE for parenchymal transection.	local anesthesia with ultrasonographic guidance. Three senior interventional radiologists performed the procedures. Percutaneous RFA was performed using a StarBurst XL–Electrosurgical Device (AngioDynamics Inc., Latham, NY, USA), which is a single electrode placed centrally within the HCC nodules. The radiofrequency is usually emitted for 10 to 15 min at 100W; timing and energy varies according to the tumor size and location. The ablation process may be repeated to obtain an entire treated area of at least 1 cm around the edges of the nodule. Percutaneous MWA was performed using a Solero–Microwave Tissute Ablation Applicator	(range 13–32) in the PA group. <u>Loss-to-follow-up</u>: I: none C: none <u>Incomplete outcome data</u>:	C: 19% (p=0.34) Major (Clavien-Dindo grade 3 or above) complications, I: 4% C: 3% <u>Liver failure</u> I: 4% C: 0% (p=0.40)	robotic platform (Intuitive Surgical inc., Sunnyvale, CA, USA) by the same surgeon. No intraoperative complications or deaths occurred.

		Intervention: 24 Control: 36 <u>N total after matching</u>: I: C: <u>Important prognostic factors</u>[2]: *Age (range:* *I: 64 (48-79)* *C: 67 (20-87)* *Number of tumors (1):* *I: 100%* *C: 100%* *Tumor size (cm)* *I: 2.0 (1.0–3.0)* *C: 1.95 (1.2–3.0)* *Charlson Comorbidity Index* *I: 7* *C: 7* *Sex:* *I: 67% M* *C: 72% M*		(AngioDynamics Inc., Latham, NY, USA) for 3–6 min at 60–80 W; timing and the energy issued varied according to the tumor size and location. MWA is preferred when the lesion is close to a vessel at the preprocedural ultrasound study. In fact, MWA is related to a reduced heat "sink e ect" compared to RFA.			
Zhang, 2020	Type of study: retrospective analysis	<u>Inclusion criteria</u>: Patients with small HCC (<2,0	For hepatic/laparoscopic resection (HR), patients were placed under	For percutaneous radiofrequency ablation (PRFA) For PRFA we used computed	<u>Length of follow-up</u>: 2.0 ± 0.5-year	<u>Outcome measures and effect size (include 95%CI and p-value if available):</u>	A higher proportion of patients who received HR had

	Setting and country: China Funding and conflicts of interest: none	cm) in a hospital from July 2016 to July 2019 <u>Exclusion criteria</u>: n.a. <u>N total at baseline</u>: Intervention: 85 Control: 90 <u>N total after matching</u>: I: C: <u>Important prognostic factors</u>[2]: *Age± SD:* *I: 63.5±7.6* *C: 62.8±8.5* *Number of tumors (1):* *I: 74.1%* *C: 91.2%* *TNM stage I* *I: 71.8%* *C:93.3%* *Sex:* *I: 55% M* *C: 52% M*	general anaesthesia, a 1 cm sub-umbilical incision was made, and a trocar with a diameter of 1 cm was inserted to determine the location of the tumour. The hepatic ligament was then removed and labelled on the surface of the liver 2 cm adjacent to the tumour. Finally, we completely resected the entire hepatic segment or lobe.	tomography (CT) or magnetic resonance imaging (MRI) for ultrasonography guidance in real-time. We intercostally or subcostally inserted a 17-gauge cooled-tip electrode of 2–3 cm. The ablation procedures generally lasted 12 min with a 3 cm electrode and 6 min with a 2 cm electrode, and a power of 80 W–100 W was typically used. The lesions were assessed one and eight weeks after PRFA by CT or MRI	<u>Loss-to-follow-up</u>: I: n.a. C: n.a <u>Incomplete outcome data</u>: n.a.	<u>Complications:</u> I: 20% C: 7.78% (p=0.033) <u>Liver failure</u> I: 1.18% C: 0% (p=0.977) PRFA treatment reduced the incidence of complications compared with resection and significantly improved overall survival as well as recurrence-free survival.	liver cirrhosis and multiple tumours (C2) and exhibited higher TNM stages compared with patients who received PRFA. During the follow-up period, the patients were followed up by CT or MRI examinations every 3–4 mo in the first two years after PRFA treatment.

Ding, 2022	Type of study: retrospective analysis Setting and country: China Funding and conflicts of interest: none	HCC patients from September 1, 2013 to June 30, 2019. <u>Inclusion criteria</u>: (a) a diagnosis of HCC with pathological confirmation; (b) Barcelona Clinic Liver Cancer stage 0-A; (c) no treatment history; and (d) more than 6 months of follow-up. <u>Exclusion criteria</u>: (a) combined MWA or RFA during RH; (b) palliative treatment; and (c) switching from RH to open surgery during the operation (these patients were counted as RH failure cases but were not	Robot-assisted hepatectomy (RH), Da Vinci system was used for all operations in the RH group. When bleeding could not be controlled or the tumor could not be removed by RH, the treatment was switched from RH to open surgery	Microwave ablation (MWA) All patients in the MWA group underwent tumor puncture biopsy before treatment and enhanced MRI within 3 days after ablation to observe the ablation zone and blood supply in surrounding areas. If the ablation zone was insufficient or abnormal blood perfusion occurred around the ablation zone, these patients received re-ablation to ensure sufficient tumor inactivation.	<u>Length of follow-up</u>: 28 months <u>Loss-to-follow-up</u>: I: n.a. C: n.a. <u>Incomplete outcome data</u>: n.a.	Outcome measures and effect size (include 95%CI and p-value if available): Complications (within 90 days after treatment) Total I: 30.3% C: 32% (p=0.89) Minor (Clavien-Dindo grade II): I: 9.8% C: 4.1% (p=0.13) Severe (Clavien-Dindo grade III-V): I: 2.5% C: 0.8% (p=0.61) Severe complication (≥grade III) rates were minuscule and comparable in both groups, which meant that both RH and MWA had extremely high safety. However, the causes of complications in the two groups were different. Complications in the RH group were mainly caused by general anesthesia or massive blood	1:1 propensity score matching was adopted to adjust baseline imbalances of preoperative clinical factors between the two groups. Clinical and laboratory parameters of patients were retrieved from the hospital database.

		included in the final analysis). <u>N total at baseline</u>: Intervention: 161 Control: 240 <u>N total after matching</u>: I: 122 C 122 <u>Important prognostic factors</u>[2]: *Age± SD:* *I:* 58.94±10.21 *C:* 58.61±11.25 *Tumor size (cm)* *I:* 2.94±1.12 *C:* 2.85±1.07 Multiple tumor I: 6.6% C: 4.1% *Charlson Comorbidity Index 0* *I: 62.3%* *C: 59%* *Sex:* *I: 83.6%M*				transfusion, while in the MWA group, the cause of complications was mainly due to the puncture process. no significant difference in total complications, minor complications or severe complications between the two groups in the crude, matched, or weighted cohort	

		C: 85.2%M					
Conticchio, 2021	Type of study: multicentric retrospective study Setting and country: Europe (France; Spain; Switzerland; Italy) Funding and conflicts of interest: none	<u>Inclusion criteria</u>: Patients who underwent Laparoscopic liver resection (LLR) or radiofrequency ablation (RFA) between 2009 and 2019. Only Child-Pugh class A and B patients aged ≥70 years who had a single HCC with a ≤3 cm diameter, without any evidence of major portal/hepatic vein branch invasion and extrahepatic disease. <u>N total at baseline</u>: Intervention: 86 Control: 98 <u>N total after matching</u>: I: 58 C: 58	The surgical strategy was tailored based on tumor size, position, and liver function. The type of liver resection was defined according to the Brisbane Classification.7 Trocars position and size were based on tumor location. Intraoperative ultrasonography was used routinely. Liver parenchymal transection was performed with various advanced instruments such as the laparoscopic cavitation ultrasonic surgical aspirator ultrasonic, bipolar, and integrated energy devices. Minor resection was defined as the resection of two or fewer Couinaud's liver segments, and major resection was defined as the resection of three or more liver segments. Pringle's maneuver was used during hepatectomy to control intraoperative bleeding. The specimen	RFA was performed using an internally cooled electrode. Depending on the tumor size and position, either a single or clustered electrode was used for ablation under ultrasound guidance, either percutaneously or using a laparoscopic or an open approach. The procedure was performed under local anesthesia and intravenous sedation for percutaneous ablation, and general anesthesia was used for laparoscopic and open ablations.	<u>Length of follow-up</u>: n.a. <u>Loss-to-follow-up</u>: I: n.a. C: n.a. <u>Incomplete outcome data</u>: n.a.	Outcome measures and effect size (include 95%CI and p-value if available): Complications (within 90 days after treatment) Total I: 30.3% C: 32% (p=0.06) Minor (Clavien-Dindo grade I-II): I: 91% C: 100% Severe (Clavien-Dindo grade III-V): I: 9% C: 0% Liver failure: I: 10% C: 2% (p=0.11) The complication rate is similar in both therapeutic strategies.	The type of treatment was planned in multidisciplinary team discussions including surgeons, hepatologists, oncologists, interventional radiologists, and pathologists. Nodules with a median size of 30 mm, located in anterolateral segments,2–6 and in contact with Glissonian pedicles represent an indication for the laparoscopic approach. 1:1 propensity score matching was performed to decrease selection bias by building a matched group of patients. Variables entered in our propensity model included age, comorbidities 2, ASA score, BMI, Child-Pugh and MELD scores, and the presence of ascites or portal hypertension.

		Important prognostic factors[2]: *Age (range):* *I: 7*5.4 (69.5–86.5) *C:* 74 (70–87) *Tumor size (cm)* *I: 3.0 (1.0–3.0)* *C: 2.0 (1.2–3.0)* Comorbidities >2 I: 40% *C: 60%* *Sex:* *I: 76%M* *C: 64%M*	was placed in an endobag and extracted from one of the trocars' introduction sites.				

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
Cheng, 2022	Definitely yes	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Probably yes	Probably no	**Low**
Magistri, 2020	Probably yes	Probably yes	Probably yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	**Some concerns**
Zhang, 2020	Probably yes	Probably yes	Probably yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	**Some concerns**
Ding, 2022	Definitely yes	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Probably yes	Probably yes	**Low**
Conticchio, 2021	Definitely yes	Probably yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Probably yes	Probably yes	**Low**

Page Break

Table of excluded studies

Reference	Reason
Si MB, Yan PJ, Hao XY, Du ZY, Tian HW, Yang J, Han CW, Yang KH, Guo TK. Efficacy and safety of radiofrequency ablation versus minimally invasive liver surgery for small hepatocellular carcinoma: a systematic review and meta-analysis. Surg Endosc. 2019 Aug;33(8):2419-2429. doi: 10.1007/s00464-019-06784-0. Epub 2019 Apr 11. PMID: 30989373.	Does not meet selection criteria: intervention too long ago
Yang S, Lin H, Song J. Efficacy and safety of various primary treatment strategies for very early and early hepatocellular carcinoma: a network meta-analysis. Cancer Cell Int. 2021 Dec 19;21(1):681. doi: 10.1186/s12935-021-02365-1. PMID: 34923980; PMCID: PMC8684647	Does not meet selection criteria: intervention too long ago
Li Z, Yu Q, Lu X, Liu Y, Ji B. Efficacy of radiofrequency ablation versus laparoscopic liver resection for hepatocellular carcinoma in China: a comprehensive meta-analysis. Wideochir Inne Tech Maloinwazyjne. 2021 Sep;16(3):455-471. doi: 10.5114/wiitm.2021.105377. Epub 2021 Apr 14. PMID: 34691297; PMCID: PMC8512513.	Does not meet selection criteria: intervention too long ago
Stippel DL, Wahba R, Bruns CJ, Bunck A, Baues C, Persigehl T. Bildgestützte minimal-invasive Chirurgie und andere lokaltherapeutische Verfahren bei primären Lebertumoren (Image-guided, minimally invasive surgery and other local therapeutic procedures for primary liver tumors). Chirurg. 2018 Nov;89(11):872-879. German. doi: 10.1007/s00104-018-0688-0. PMID: 30030546.	Wrong study type: Review article
Li X, Wu YS, Chen D, Lin H. Laparoscopic hepatectomy versus radiofrequency ablation for hepatocellular carcinoma: a systematic review and meta-analysis. Cancer Manag Res. 2019 Jun 24;11:5711-5724. doi: 10.2147/CMAR.S189777. PMID: 31417314; PMCID: PMC6600087.	Does not meet selection criteria: intervention too long ago
Tan HY, Gong JF, Yu F, Tang WH, Yang K. Long-Term Efficacy of Laparoscopic Radiofrequency Ablation in Early Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. J Laparoendosc Adv Surg Tech A. 2019 Jun;29(6):770-779. doi: 10.1089/lap.2018.0642. Epub 2019 Feb 25. PMID: 30801203.	Does not meet PICOs: different comparison
Lu X, Z. . Li, Y. . Liu, Z. . Wang, F. . Peng, Q. . Yu, X. . . Fu, and B. . Ji. "The Long-Term Efficacy of Radiofrequency Ablation Versus Laparoscopic Hepatectomy for Small Hepatocellular Carcinoma in East Asia: A Systematic Review and Meta-Analysis". Iranian Red Crescent Medical Journal, vol. 22, no. 7, July 2020, https://ircmj.com/index.php/IRCMJ/article/view/732.)	Does not meet PICOs: different outcome measures
Jin S, Tan S, Peng W, Jiang Y, Luo C. Radiofrequency ablation versus laparoscopic hepatectomy for treatment of hepatocellular carcinoma: a systematic review and meta-analysis. World J Surg Oncol. 2020 Aug 12;18(1):199. doi: 10.1186/s12957-020-01966-w. PMID: 32787883; PMCID: PMC7425008.	Does not meet PICOs: different outcome measures
Chen QF, Li W, Yu SC, Chou YH, Rhim H, Yang X, Shen L, Dong A, Huang T, Huang J, Zhang F, Fan W, Zhao M, Gu Y, Huang Z, Zuo M, Zhai B, Xiao Y, Kuang M, Li J, Han J, Song W, Ma J, Wu P. Consensus of Minimally Invasive and Multidisciplinary Comprehensive Treatment for Hepatocellular Carcinoma - 2020 Guangzhou Recommendations. Front Oncol. 2021 Jul 2;11:621834. doi: 10.3389/fonc.2021.621834. PMID: 34277397; PMCID: PMC8284077.	Wrong study type: Consensus paper
Zhu F, Chang Q, Duan S, Leng W. Efficacy and safety of radiofrequency ablation versus laparoscopic hepatectomy for small hepatocellular carcinoma: A protocol for a randomized controlled trial. Medicine (Baltimore). 2021 Jan 8;100(1):e23678. doi: 10.1097/MD.0000000000023678. PMID: 33429736; PMCID: PMC7793421.	Wrong study type: Study protocol for RCT
Shiina S, Sato K, Tateishi R, Shimizu M, Ohama H, Hatanaka T, Takawa M, Nagamatsu H, Imai Y. Percutaneous Ablation for Hepatocellular Carcinoma: Comparison of Various Ablation Techniques and Surgery. Can J Gastroenterol Hepatol. 2018 Jun 3;2018:4756147. doi: 10.1155/2018/4756147. PMID: 29974040; PMCID: PMC6008833.	Wrong study type: Review article
Chong CC, Lee KF, Chu CM, Chan AW, Yu SC, Lai PB. Laparoscopic Hepatectomy (with or without Robotic Assistance) versus Radiofrequency Ablation as a Minimally Invasive Treatment for Very Early-Stage or Early-Stage Hepatocellular Carcinoma. Dig Surg. 2020;37(1):65-71. doi: 10.1159/000497112. Epub 2019 Mar 27. PMID: 30917378.	Does not meet selection criteria: intervention too long ago
Ryu T, Takami Y, Wada Y, Hara T, Sasaki S, Saitsu H. Hepatic resection versus operative microwave ablation for single hepatocellular carcinoma ≤5 cm: A propensity score-matched analysis. Surgery. 2019 Sep;166(3):254-262. doi: 10.1016/j.surg.2019.05.007. Epub 2019 Jul 3. PMID: 31279438.	Does not meet selection criteria: intervention too long ago
Jiang YQ, Wang ZX, Deng YN, Yang Y, Wang GY, Chen GH. Efficacy of Hepatic Resection versus. Radiofrequency Ablation for Patients With Very-Early-Stage or Early-Stage Hepatocellular Carcinoma: A Population-Based Study With Stratification by Age and Tumor Size. Front Oncol. 2019 Feb 26;9:113. doi: 10.3389/fonc.2019.00113. PMID: 30863723; PMCID: PMC6400103.	Does not meet PICOs: different outcome measures

Liu H, Wan X, Fu K, Wang B, Fu X, Zhang C, Journal of Interventional Radiology (China) 2019. doi: 10.3969/j.issn.1008-794X.2019.010.018. Epub 2019 Dec 12. PUI: L630007305.	Full text publication unavailable
Hsiao CY, Hu RH, Ho CM, Wu YM, Lee PH, Ho MC. Surgical resection versus radiofrequency ablation for Barcelona Clinic Liver Cancer very early stage hepatocellular carcinoma: long-term results of a single-center study. Am J Surg. 2020 Oct;220(4):958-964. doi: 10.1016/j.amjsurg.2020.03.017. Epub 2020 Mar 25. PMID: 32247523.	Does not meet PICOs: different outcome measures
Di Sandro S, Benuzzi L, Lauterio A, Botta F, De Carlis R, Najjar M, Centonze L, Danieli M, Pezzoli I, Rampoldi A, Bagnardi V, De Carlis L. Single Hepatocellular Carcinoma approached by curative-intent treatment: A propensity score analysis comparing radiofrequency ablation and liver resection. Eur J Surg Oncol. 2019 Sep;45(9):1691-1699. doi: 10.1016/j.ejso.2019.04.023. Epub 2019 Apr 29. PMID: 31072620.	Does not meet selection criteria: intervention too long ago
Pan YX, Long Q, Yi MJ, Chen JB, Chen JC, Zhang YJ, Xu L, Chen MS, Zhou ZG. Radiofrequency ablation versus laparoscopic hepatectomy for hepatocellular carcinoma: A real world single center study. Eur J Surg Oncol. 2020 Apr;46(4 Pt A):548-559. doi: 10.1016/j.ejso.2019.10.026. Epub 2019 Oct 24. PMID: 31677940.	Does not meet PICOs: different populations (tumors ≥5cm)
Lin CH, Ho CM, Wu CH, Liang PC, Wu YM, Hu RH, Lee PH, Ho MC. Minimally invasive surgery versus radiofrequency ablation for single subcapsular hepatocellular carcinoma ≤ 2 cm with compensated liver cirrhosis. Surg Endosc. 2020 Dec;34(12):5566-5573. doi: 10.1007/s00464-019-07357-x. Epub 2020 Jan 28. PMID: 31993821.	Does not meet selection criteria: intervention too long ago
Liu YW, Yen YH, Li WF, Wang CC, Lu SN, Kee KM, Yong CC, Cheng YF, Wang JH, Hu TH, Hung CH, Chen CH. Minimally invasive surgery versus percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma: Results from a high-volume liver surgery center in East Asia. Surg Oncol. 2022 Jun;42:101769. doi: 10.1016/j.suronc.2022.101769. Epub 2022 Apr 19. PMID: 35468499.	Does not meet PICOs: Patients were preselected (not applicable for MIS)
Wang, Zhen and Liu, Miao and Zhang, De-Zhi and Wu, Song-Song and Hong, Zhi-Xian and He, Guang-Bin and Yang, Hong and Xiang, Bang-de and Li, Xiao and Jiang, Tian-An and Li, Kai and Tang, Zhe and Huang, Fei and Lu, Man and Chen, Ji-An and Lin, Yu-Cheng and Lu, Xiao and Wu, Yu-Quan and Zhang, Xiao-Wu and Zhang, Ye-Fan and Cheng, Chao and Ye, Huo-Lin and Wang Z, Liu M, Zhang DZ, Wu SS, Hong ZX, He GB, Yang H, Xiang BD, Li X, Jiang TA, Li K, Tang Z, Huang F, Lu M, Chen JA, Lin YC, Lu X, Wu YQ, Zhang XW, Zhang YF, Cheng C, Ye HL, Wang LT, Zhong HG, Zhong JH, Wang L, Chen M, Liang FF, Chen Y, Xu YS, Yu XL, Cheng ZG, Liu FY, Han ZY, Tang WZ, Yu J, Liang P. Microwave ablation versus laparoscopic resection as first-line therapy for solitary 3-5-cm HCC. Hepatology. 2022 Jul;76(1):66-77. doi: 10.1002/hep.32323. Epub 2022 Jan 28. PMID: 35007334.	Wrong study type: Conference abstract
Lee DH, Kim JW, Lee JM, Kim JM, Lee MW, Rhim H, Hur YH, Suh KS. Laparoscopic Liver Resection versus Percutaneous Radiofrequency Ablation for Small Single Nodular Hepatocellular Carcinoma: Comparison of Treatment Outcomes. Liver Cancer. 2021 Feb;10(1):25-37. doi: 10.1159/000510909. Epub 2021 Jan 14. PMID: 33708637; PMCID: PMC7923879.	Does not meet selection criteria: intervention too long ago
Ogiso S, Seo S, Eso Y, Yoh T, Kawai T, Okumura S, Ishii T, Fukumitsu K, Taura K, Seno H, Uemoto S. Laparoscopic liver resection versus percutaneous radiofrequency ablation for small hepatocellular carcinoma. HPB (Oxford). 2021 Apr;23(4):533-537. doi: 10.1016/j.hpb.2020.08.009. Epub 2020 Sep 7. PMID: 32912835.	Does not meet selection criteria: intervention too long ago
Xu H, Zhou L, Jin Q. The effects of ultrasound-guided radiofrequency ablation and laparoscopic hepatectomy in the treatment of small hepatocellular carcinoma: a retrospective analysis. Transl Cancer Res. 2021 Nov;10(11):4794-4801. doi: 10.21037/tcr-21-367. PMID: 35116332; PMCID: PMC8798287.	Does not meet PICOs: different populations (tumors ≥6cm)
Kim S, Yoon CJ, Cho JY, Han HS, Yoon YS, Lee HW, Lee JS, Kim M, Lee B, Ahn S. Comparative long-term outcomes of laparoscopic hepatectomy and radiofrequency ablation for hepatocellular carcinoma located in the anterolateral segments of the liver. J Hepatobiliary Pancreat Sci. 2022 Mar;29(3):349-358. doi: 10.1002/jhbp.1064. Epub 2021 Nov 2. PMID: 34689415.	Does not meet selection criteria: intervention too long ago
Wang L, Deng D, Deng C. Clinical efficacy and long-term prognosis of laparoscopic liver resection and radiofrequency ablation for small hepatocellular carcinoma. International Journal of Clinical and Experimental Medicine 2020 May;13(10):7349-7356. PUI: L2005380081.	Does not meet selection criteria: intervention too long ago

Literature search strategy

Algemene informatie

Richtlijn: NVMDL hepatocellulair carcinoom	
Uitgangsvraag: UV11 Is minimaal invasieve chirurgie (robot of laparoscopie) te prefereren boven ablatie (gestratificeerd per segment)?	
Database(s): Ovid/Medline, Embase	Datum: 4-4-2022, 27-6-2022
Periode: 2016-	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: **27-6-2022** Op basis van de zoekstrategie van 4 april wordt onvoldoende evidence gevonden. Omdat een relevante SR uit 2020 wordt gevonden, worden aanvullende observationele studies vanaf 2019 toegevoegd. Ook is de zoekstrategie aangevuld met SRs en de RCTs vanaf 4 april. De resultaten zijn ontdubbel t.o.v. het reeds eerder gevonden resultaat. **4-4-2022** Voor deze vraag is gezocht met de volgende elementen: Hepatocellulair carcinoom EN (robot assisted surgery OF minimally invasive surgery OF laparoscopy) NB. Het sleutelartikel wordt wel gevonden in de basis set maar niet in de uiteindelijke set omdat het om een observationele studie gaat en niet SR of RCT	
Te gebruiken voor richtlijnen tekst: In de databases Embase en Ovid/Medline is op 27-6-2022 met relevante zoektermen gezocht naar systematische reviews en RCTs over minimale invasieve, robot chirurgie of laparosopie bij hepatocellulair carcinoom. De literatuurzoekactie leverde 754 unieke treffers op.	

Zoekopbrengst

27-6-2022	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld t.o.v. strategie 4-4-2022**
SRs	111	80	5
RCTs	71	38	5
Observationele studies vanaf 2019	537	448	565
Overig			
Totaal			**754**
4-4-2022	**EMBASE**	**OVID/MEDLINE**	**Ontdubbeld**
SRs	106	78	127
RCTs	65	37	52
Observationele studies			
Overig			
Totaal			179

5

Zoekstrategie

Embase 27-6-2022

No.	Query	Results
#18	#17 AND (#7 OR #8) OBS	537
#17	#3 AND (1-1-2019)/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)	906
#16	#9 OR #10	145
#15	#10 NOT #9	29
#14	#11 AND #12	1

#13	#4 AND #12	1
#12	(laparoscopic AND hepatectomy AND robotic AND assistance AND versus AND ra diofrequency AND ablation AND as AND a AND minimally AND invasive AND treat ment AND for AND very AND 'early stage' OR 'early stage') AND hepatocellular AND carcinoma AND chong AND 2020	1
#11	#4 AND (#7 OR #8)	784
#10	#4 AND #6 RCT	71
#9	#4 AND #5 SR	111
#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 g ender 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)))	13013362
#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	6767914

	(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)	
#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 (1-1-2016)/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)	1395
#3	#1 AND #2	3898
#2	'minimally invasive surgery'/exp OR 'robot assisted surgery'/exp OR 'laparoscopy'/exp OR laparoscop*:ti,ab,kw OR (((mini* OR robot*) NEAR/3 surg*):ti,ab,kw)	344570
#1	'liver cell carcinoma'/exp OR ('liver cancer'/de AND 'primary tumor'/exp) OR ((hepat* NEAR/3 carcinom*):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw OR ((primary NEAR/2 liver):ti,ab,kw)	238590

Embase 4-4-2022

No.	Query	Results
#15	(#9 OR #10) AND #12 Sleutelartikel niet gevonden in SRs, RCT	0
#14	#11 AND #12 Sleutelartikel gevonden in observationele studies	1
#13	#4 AND #12	1
#12	(laparoscopic AND hepatectomy AND robotic AND assistance AND versus AND radiofrequency AND ablation AND as AND a AND minimally AND invasive AND treatment AND for AND very AND 'early stage' OR 'early stage') AND hepatocellular AND carcinoma AND chong AND 2020	1
#11	#4 AND (#7 OR #8)	784

#10	#4 AND #6 RCT	65
#9	#4 AND #5 SR	106
#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)))	13013362
#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 (1-1-2016)/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)	1330
#3	#1 AND #2	3898
#2	'minimally invasive surgery'/exp OR 'robot assisted surgery'/exp OR 'laparoscopy'/exp OR laparoscop*:ti,ab,kw OR (((mini* OR robot*) NEAR/3 surg*):ti,ab,kw)	344570
#1	'liver cell carcinoma'/exp OR ('liver cancer'/de AND 'primary tumor'/exp) OR ((hepat* NEAR/3 carcinom*):ti,ab,kw) OR hepatocarcinom*:ti,ab,kw OR hepatoma:ti,ab,kw OR ((primary NEAR/2 liver):ti,ab,kw)	238590

Ovid/Medline 27-6-2022

#	Searches	Results
14	11 and (12 or 13) OBS	448
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	5185679

	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.))	
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 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)	4180171
11	limit 3 to yr="2019 - Current"	811
10	9 not 8 RCT	38
9	6 and 7	66
8	5 and 7 SR	80
7	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1316
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.) not (animals/ not humans/)	1386546
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 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/))	573240
4	limit 3 to yr="2016 - 2022"	1385
3	1 and 2	3726
2	exp Minimally Invasive Surgical Procedures/ or exp Laparoscopy/ or Robotic Surgical Procedures/ or laparoscop*.ti,ab,kf. or ((robot* or mini*) adj3 surg*).ti,ab,kf.	650928

1	Carcinoma, Hepatocellular/ or (hepat* adj3 carcinom*).ti,ab,kf. or hepatocarcinom*.ti,ab,kf. or hepatoma.ti,ab,kf. or (liver adj3 primary).ti,ab,kf.	164919

Ovid/Medline 4-4-2022

#	Searches	Results
10	9 not 8 RCT	37
9	6 and 7	64
8	5 and 7 SR	78
7	4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/)	1252
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.) not (animals/ not humans/)	1363719
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 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/))	556325
4	limit 3 to yr="2016 - 2022"	1318
3	1 and 2	3659
2	exp Minimally Invasive Surgical Procedures/ or exp Laparoscopy/ or Robotic Surgical Procedures/ or laparoscop*.ti,ab,kf. or ((robot* or mini*) adj3 surg*).ti,ab,kf.	642100
1	Carcinoma, Hepatocellular/ or (hepat* adj3 carcinom*).ti,ab,kf. or hepatocarcinom*.ti,ab,kf. or hepatoma.ti,ab,kf. or (liver adj3 primary).ti,ab,kf.	162233

5

Module 11.1 Gevolgen en aanpak eerste jaar

Uitgangsvraag

Wat is de optimale aanpak voor het signaleren van lichamelijke of psychosociale klachten bij patiënten met een hepatocellulair carcinoom?

Inleiding

Deze module geeft inzicht het belang van vroegtijdige signalering van klachten die patiënten kunnen ontwikkelen na diagnose en eventuele behandeling van een hepatocellulair carcinoom. Screening en detectie van deze klachten met een gevalideerd instrument zijn hierbij essentieel.

Zoeken en selecteren

Er is voor deze vraag geen systematische literatuuranalyse uitgevoerd. De aanbevelingen zijn gebaseerd op expert opinion van de expertisegroep, waar mogelijk onderbouwd met literatuur die door de expertisegroep leden is aangedragen.

Overwegingen

Ziekte en behandeling hebben grote gevolgen

De Gezondheidsraad concludeert dat veel patiënten, na een in opzet curatieve behandeling voor kanker, met klachten kampen (Gezondheidsraad, 2007). Deze klachten kunnen beperkt dan wel uitgebreid zijn, zowel van lichamelijke als psychische aard zijn, en vroeg dan wel later optreden. Dit wordt 'distress genoemd. Met distress wordt bedoeld: een onplezierige emotionele ervaring van psychologische (cognitief, gedragsmatig, emotioneel), sociale en/of spirituele aard die kan interfereren met het vermogen om effectief om te gaan met kanker, de daarbij horende fysieke symptomen en de behandeling (Richtlijn detecteren behoefte psychosociale zorg, 2017). Het gaat hierbij veelal om lichamelijke gevolgen die duidelijk verbonden zijn aan de specifieke aard van de kanker, gevolgen van de behandeling, psychosociale problemen en algemene klachten. Algemene problemen kunnen zijn op het gebied van relaties met partner en gezin, sociale contacten, problemen met maatschappelijke participatie, arbeidsparticipatie en financiële problemen.

Vroege gevolgen

Vroege gevolgen zijn die gevolgen die de patiënt direct na diagnose en tijdens behandeling of in de eerste periode (tot één jaar) na de behandeling ervaart. De Gezondheidsraad stelt dat tijdige behandeling door vroege signalering, de ziektelast van vroege gevolgen kan verminderen. De zorg met betrekking tot vroege gevolgen valt primair onder de verantwoordelijkheid van de behandelend specialist. Uiteraard kunnen hierbij andere hulpverleners ingeschakeld worden.

Patiënten met een HCC hebben in een vroeg stadium van de ziekte over het algemeen geen klachten. Voorbeelden van klachten bij een verder gevorderd stadium zijn vermoeidheid, buikpijn, slechte eetlust, misselijkheid/braken, gewichtsverlies (Sun, 2008).

Patiënten met een cirrose hebben een verhoogd risico op een HCC. De vroege gevolgen voor deze groep patiënten zijn vaak gerelateerd aan leverfalen. Symptomen van leverfalen zijn icterus, ascites, jeuk, vermoeidheid en *encefalopathie*.

Psychische klachten die voorkomen zijn problemen met concentratie en geheugen, angst, depressie, woede, verdriet, verminderd zelfbeeld, vermoeidheid, eenzaamheid, twijfels over

de prognose en psychische problemen met betrekking tot controles (zie richtlijn ‘Herstel na Kanker').

Signalering

Nazorg begint met het systematisch signaleren van klachten. Een basis set van klachtensignalering dient bij elke patiënt standaard toegepast te worden. In de richtlijn ‘Detecteren van behoefte aan psychosociale zorg' (2017) worden de signaleringsinstrumenten de Lastmeter en de EORTC QLQ-C30 als meest geschikte instrumenten aanbevolen in Nederland om distress te signaleren bij volwassen mensen met kanker. Hierbij lijkt de Lastmeter aan de meeste eisen, voorwaarden en kenmerken te voldoen. De literatuursearch toont dat de geschiktheid van de Lastmeter voor screening en signalering het grootst is (Richtlijn detecteren behoefte psychosociale zorg, 2017). De geschiktheid van de EORTC QLQ- C30 voor monitoring is beter aangetoond. Voor het HCC is er specifiek de EORTC QLQ HCC 18. De behandelaar is verantwoordelijk voor het screenen naar distress in de verschillende fasen. Een opzet zoals beschreven in module 7.3 kan hierbij gehanteerd worden.

Zelfmanagement

Veel nazorg betekent zelfzorg door de patiënt. Zorgprofessionals, zeker verpleegkundigen/verpleegkundig specialisten, hebben de belangrijke taak de patiënt te ondersteunen in deze zelfzorg, het zogenaamde zelfmanagement. Informatie over diagnose en behandeling blijkt meestal goed voorhanden, maar informatie betreffende psychosociale gevolgen, gevolgen op langere termijn, leefstijl en financiële consequenties is vaak niet toereikend.

Bij de patiëntenvereniging kan men terecht voor informatie, vragen en belangenbehartiging. Patiënten met een HCC kunnen terecht bij de Nederlandse Leverpatiënten Vereniging. Leefstijladviezen en -interventies kunnen de kwaliteit van leven van patiënten bevorderen en kunnen mogelijk het risico op late gevolgen van kanker en op andere ziekten verlagen (Demark-Wahnefried, 2006).

Behandeling

Naast de standaardbegeleiding, zoals voorlichting, steun en advies bij zelfzorg, zijn verschillende behandelingen voor specifieke lichamelijke-, psychische- en sociale gevolgen van kanker effectief gebleken.

Voor de behandeling van pijn wordt verwezen naar de richtlijn ‘Pijn bij patiënten met kanker’. In de richtlijn ‘Algemene voedings- en dieetbehandeling' is aandacht voor slechte eetlust, misselijkheid/braken, en gewichtsverlies (NVD, 2017).

De symptomen van leverfalen dienen door een ervaren hepatoloog behandeld te worden.

De adviezen uit richtlijn ‘Chronische Jeuk' (2022) kunnen ondersteunend zijn in de behandeling van jeuk.

Naast behandeling van specifieke klachten zijn psychologische behandeling en oncologische revalidatie in te zetten bij klachten en ter verbetering van de kwaliteit van leven. In de richtlijn ‘Oncologische revalidatie' zijn beslisbomen opgenomen voor de verwijzing en revalidatie bij specifieke klachten.

Aanbevelingen

Aanbeveling-1: Systematische aanpak van vroege gevolgen

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

De vroege gevolgen van kanker (zowel fysiek als psychosociaal) vergen een systematische aanpak.

Informeer patiënten en familie/naasten over het eventueel ontstaan van klachten na behandeling van HCC. Signaleer deze vroege gevolgen van kanker met behulp van een (gevalideerd) screeningsinstrument. Deze screening dient te worden ingezet vanaf de diagnose tot aan de behandeling en follow-up.

Kennislacunes

Hier onderzoeksvraag opnemen (dit kan de zoekvraag (PICO) zijn) …

Literatuur

Demark-Wahnefried W, Pinto BM, Gritz ER. Promoting health and physical functioning among cancer survivors: potential for prevention and questions that remain. J Clin Oncol. 2006; 24(32): 5125-31.

Gezondheidsraad Nacontrole in de oncologie. Doelen onderscheiden, inhoud onderbouwen. 2007; maart 27.

NVA. Richtlijn pijn bij patiënten met kanker. 2019. https://richtlijnendatabase.nl/richtlijn/behandeling_van_pijn_bij_patienten_met_kanker/beleid_en_behandeling_bij_pijn_bij_kanker.html

NVD. Richtlijn: Algemene Voedings- en dieetbehandeling. 2017. https://nvdietist.nl/app/uploads/2021/03/Algemene_Voedings-_en_dieetbehandeling_.pdf

NVPO. Richtlijn detecteren behoefte psychosociale zorg. 2017. https://richtlijnendatabase.nl/richtlijn/detecteren_behoefte_psychosociale_zorg/algemeen.html

NVDV. Richtlijn Chronische jeuk. 2022. https://richtlijnendatabase.nl/richtlijn/chronische_jeuk/startpagina_chronische_jeuk.html

Sun VC, Sarna L. Symptom management in hepatocellular carcinoma. Clin J Oncol Nurs. 2008; Oct 12(5):759-66. doi: 10.1188/08.CJON.759-66.

Bijlagen bij hoofdstuk 11.1

Evidencetabellen
Niet van toepassing.

Exclusietabel
Niet van toepassing.

Zoekverantwoording
Niet van toepassing.

Module 11.2 Detectie nieuwe kankermanifestaties

Uitgangsvraag

Wat is de optimale organisatie van vroege detectie van nieuwe manifestaties van kanker bij patiënten met hepatocellulair carcinoom?

Inleiding

Het vroeg detecteren van de ontwikkeling van een recidief HCC kan zinvol zijn voor patiënten die een behandeling hebben ondergaan voor een HCC. Het kan leiden tot winst in kwaliteit van leven of overlevingsduur. Deze detectie dient plaats te vinden via een follow-up schema.

Zoeken en selecteren

Er is voor deze vraag geen systematische literatuuranalyse uitgevoerd. De aanbevelingen zijn gebaseerd op expert opinion van de expertisegroep, waar mogelijk onderbouwd met literatuur die door de expertisegroep leden is aangedragen.

Overwegingen

Vroege detectie niet altijd zinvol

Voor HCC kan vroege detectie, ook na vele jaren, winst in duur of kwaliteit van leven kan opleveren (Jefferey, 2007; Lu, 2009). Afhankelijk van de presentatie van het recidief, de conditie en leeftijd van patiënt zal in een multidisciplinair overleg verder beleid worden bepaald. Het is aan het multidisciplinair overleg te bepalen of een aanvullende behandeling kan worden uitgevoerd zonder de kwaliteit van leven kan verminderen en de ziektelast kan verhogen.

Studie van Uka (2007) laat zien dat van de 995 patienten met diagnose HCC, 151 patienten metastasen ontwikkelden. 68 patiënten (45%) ontwikkelde metastasen bij presentatie ten tijd van de HCC en 83 patiënten (55%) ontwikkelde metastasen gedurende de follow-up waarbij het grootste gedeelte longmetastasen betrof (47%) (Uka, 2007).

Detectie alleen bij betere overleving

De Gezondheidsraad geeft in haar rapport aan dat vroege detectie van nieuwe manifestaties van kanker alleen dient plaats te vinden bij winst in duur of kwaliteit van leven (Gezondheidsraad, 2007). De winst is in een vroeg stadium effectiever dan in een later stadium als er klachten ontstaan. De vroege detectie moet alleen worden uitgevoerd in een programmatische aanpak. Deskundige evaluatie van de literatuur en de vertaalslag naar een verstandig oordeel is nodig.

Voor patiënten die een behandeling voor HCC ondergaan hebben is vroege detectie van een lokaal recidief of de novo tumor zinvol, aangezien kleine tumoren lokaal behandeld kunnen worden. Als het primaire HCC gepaard ging met een verhoogd alfa-FoetoProteine (AFP) kan AFP in de follow-up gebruikt worden ter detectie van recidief ziekte.

Een voorbeeld van een voor follow-up is weergegeven in tabel 1. Voor vroeg detectie van het HCC wordt geadviseerd, zoals weergegeven in tabel 11.2.1 iedere drie maanden het alfa-FoetoProteïne (AFP) te bepalen. Daarnaast wordt geadviseerd ieder half jaar een CT lever-scan of MRI lever te verrichten.

Na vijf jaar kan de detectie voor patiënten met een cirrose hervat worden zoals aanbevolen in de module Surveillance. Voor patiënten zonder cirrose kan de follow-up beëindigd worden.

Tabel 11.2.1 Detectie van nieuwe manifestaties van HCC

Maanden	Serum AFp bepalen	CT/ MRI lever verrichten
3	X	X
6	X	X inclusief thorax
9	X	X
12	X	X inclusief thorax
18	X	X
24	X	X inclusief thorax
Jaar 2-5 á 6 maanden	X	X inclusief thorax

Waarden en voorkeuren van patiënten

De resultaten van studies naar patiënten preferenties voor nazorg en nacontrole zijn niet eenduidig. Uit sommige onderzoeken blijkt dat patiënten meer follow-up willen (omdat deze consulten voor de geruststelling zorgen dat 'alles goed is'). Uit andere onderzoeken blijkt dat zij minder follow-up willen. Er kan wel geconcludeerd worden dat patiënten duidelijke en eenduidige informatievoorziening over de behandeling en nazorg belangrijk vinden (Hamajima, 1996; Katsumura, 2008).

Voorlichting noodzakelijk

Het rapport van de Gezondheidsraad geeft aan dat er structurele aandacht moet zijn voor genuanceerde voorlichting over de mogelijkheden en beperkingen van vroege detectie van nieuwe manifestaties van kanker. Transparantie over de beperkingen bij de behandeling van een recidief is van belang alvorens onderzoek naar het opsporen van onbehandelbare ziekte te starten. Het voorkomt valse hoop en gaat onnodige medicalisering tegen.

Aanbevelingen

Aanbeveling-1

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

Bij patiënten met (verdenking op) HCC dient vroege detectie van nieuwe manifestaties van kanker plaats te vinden aangezien er voldoende wetenschappelijk bewijs is dat deze detectie tot winst in duur of kwaliteit van leven kan leiden. De winst is in een vroeg stadium effectiever dan in een later stadium als er klachten ontstaan. De comorbiditeit en conditie van patiënt dienen in overweging te worden genomen bij het uitvoeren van surveillance.

Het is te overwegen bij follow-up na behandeling van HCC imaging van de lever altererend te combineren met een CT Thorax.

Gebruik voor patiënten na behandeling voor HCC het volgende follow-up schema:

Maanden	Serum AFp bepalen	CT/ MRI lever verrichten
3	X	X
6	X	X inclusief thorax
9	X	X
12	X	X inclusief thorax
18	X	X
24	X	X inclusief thorax
Jaar 2-5 á 6 maanden	X	X inclusief thorax

Overweeg bij follow-up na behandeling van HCC imaging van de lever altererend te combineren met een CT Thorax.

Literatuur

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Bijlagen bij hoofdstuk 11.2

Evidencetabellen
Niet van toepassing.

Exclusietabel
Niet van toepassing.

Zoekverantwoording
Niet van toepassing.

Module 12.1 Organisatie diagnostiek bij focale leverafwijking verdacht voor maligniteit (HCC)

Uitgangsvraag

Wat is de optimale organisatie van diagnostiek bij een patiënt met een verdenking van een focale afwijking of hepatocellulair carcinoom?

Inleiding

Alle patiënten met de verdenking op een HCC dienen te worden besproken in een multidisciplinair overleg. Deze expertise groep komt minimaal één keer per week samen om diagnostiek en behandeldoelen te bespreken. Voorafgaand aan de aanmelding van het MDO dient beschikbare informatie over laboratoriumuitslagen, afbeeldend en histologisch onderzoek in de verwijzing opgenomen te zijn. Na bespreking & notulering van diagnose en behandeladvies in het MDO dient terugkoppeling aan de patiënt, huisarts en verwijzend specialist plaats te vinden. Poliklinische beoordeling en bespreking van het opgestelde behandeladvies dient met patiënt, familie en naasten besproken te worden.

Zoeken en selecteren

Er is voor deze vraag geen systematische literatuuranalyse uitgevoerd. De aanbevelingen zijn gebaseerd op expert opinion van de expertisegroep, waar mogelijk onderbouwd met literatuur die door de expertisegroep leden is aangedragen.

Overwegingen

Er is geen systematische search gedaan en derhalve is er geen literatuur uitgewerkt. De werkgroep is van mening dat de volgende zaken belangrijk zijn in het diagnostisch traject van een patiënt met (verdenking van) een focale leverafwijking (HCC).

Multidisciplinair overleg

Tijdens het MDO worden de diagnostische bevindingen gezamenlijk besproken. Aanwezig zijn minimaal:

- MDL-arts
- Hepatobiliair/ transplantatie chirurg
- Interventie radioloog
- Abdomen radioloog
- Radiotherapeut
- Internist-oncoloog
- Verpleegkundig specialist
- Nucleair geneeskundige
- Patholoog (op afroep bij casuïstiek)
- Internist- Endocrinoloog (op afroep bij casuïstiek)
- Notulist

Het doel van het MDO in deze fase is:

- Het opstellen van het nadere diagnostisch beleid wanneer onzekerheid over de diagnose bestaat dan wel met grote zekerheid gezamenlijk vaststellen dat het geen maligniteit betreft.
- Het opstellen van een zo goed mogelijk behandelplan en harmonisatie van de begeleiding in geval er sprake is van een maligne levertumor.
- Het bespreken van patiënten waarbij metastasen zijn vastgesteld.

- Andere situaties op gebied van leverpathologie, waarbij multidisciplinaire afstemming gewenst is.
- Het fungeren als expert centrum voor andere centra of multidisciplinaire overleggen.

Poliklinisch consult

Het opstellen van het beleid in geval van onzekerheid over de diagnose: bepalen of nadere diagnostiek noodzakelijk is of dat met grote zekerheid gezamenlijk vastgesteld kan worden of het wel of geen maligniteit betreft. De diagnostiek van een voor maligniteit verdachte focale afwijking in de lever dient plaats te vinden met een beperkte wachttijd. Het poliklinische traject is op een dergelijke wijze georganiseerd, dat alle reeds verrichte diagnostische onderzoeken (anamnese, onderzoek, lab, onderzoek, eerste revisie elders verricht beeldmateriaal, aanvullend beeldvormend onderzoek) op één dag worden besproken kunnen worden uitgevoerd. Maximaal 21 dagen na de eerste presentatie moet het behandelplan opgesteld zijn (NZA, 2017).

In alle gevallen geldt, dat het aantal bezoeken aan deze polikliniek tot een minimum beperkt dient te blijven. Vaak kan na de wekelijkse MDO de uitslag verteld worden. Dit geldt vooral voor patiënten bij wie geen afwijkingen worden aangetoond of waar een benigne afwijking aangetoond wordt. Steeds wordt gestreefd naar het minimaliseren van de tijd tussen de diagnostische tests en het geven van de uitslagen. Deze consulten kunnen bestaan uit fysieke, telefonische of e-consulten.

Begeleiding

De diagnose *maligniteit* dient op professionele wijze door de behandelaar aan de patiënt te worden verteld. Het verdient aanbeveling om patiënten een naaste mee te laten nemen, wanneer de uitslagen besproken worden. Het behandelteam betreft een medisch- (hoofdbehandelaar) of verpleegkundig specialist (medebehandelaar).

Deze geeft tijdens dit gesprek voorlichting, steun en begeleiding bij het nemen van een beslissing over de behandeling. Vervolgafspraken worden gemaakt en de patiënt dient te weten hoe en bij welke vragen of problematiek betrokken professionals van de leverwerkgroep te bereiken zijn. Bij voorkeur wordt de coördinerende rol bij de verpleegkundig specialist gelegd.

Zorgpad organisatie

Conform de ‘Wet op de Geneeskundige Behandelings Overeenkomst' (WGBO) moet er voldoende tijd uitgetrokken worden om de verschillende pre-behandeling onderzoeken met de patiënt te bespreken alsook waarom men wel of niet voor bepaalde onderzoeken in aanmerking komt. Het moet de patiënt duidelijk zijn, waar deze zich kan vervoegen als er nog vragen zijn. Uit onderzoek blijkt dat een verpleegkundig specialist bij uitstek geschikt is als coördinator van de diagnostiek op de polikliniek. In deze rol kan zij als aanspreekpunt optreden, wat een verbetering kan geven van de continuïteit en kwaliteit van zorg. Het diagnostisch traject kan complex zijn en dient de patiënt te worden uitgelegd. Het verdient aanbeveling de stappen in het zorgpad expliciet te maken door het zorgpad te beschrijven inclusief gewenste normtijden voor de stappen in het zorgpad.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>

Vertegenwoordigers van verschillende medische specialismen die expertise hebben op het gebied van diagnostiek en behandeling van levertumoren (zoals weergegeven bij het multidisciplinair overleg) moeten aanwezig zijn om alle mogelijkheden te kunnen bespreken. Door recente ontwikkelingen op gebied van de behandeling van levertumoren door

radiotherapie, is de aanwezigheid van een radiotherapeut geïndiceerd. Ook op het gebied van endocrinologische afwijkingen met uitzaaiingen in de lever, zijn er nieuwe ontwikkelingen die die de aanwezigheid van een deskundige op dit gebied (internist-endocrinoloog). Deze deskundigheid zal met name aanwezig zijn in centra met een tertiair verwijzingsprofiel. De rol van de patholoog is aan de orde wanneer afbeeldend onderzoek te kort schiet bij het stellen van de diagnose en histologische beoordeling nodig is voor het stellen van een differentiaal diagnose. De fysieke aanwezigheid van de patholoog is in de meeste gevallen niet noodzakelijk, indien de beschrijving van de bevindingen helder is.

Basis voorwaarden zijn voldoende capaciteit voor de diagnostische mogelijkheden en de uitvoering van behandelvoorstellen.

Er moet een overlegruimte beschikbaar zijn met audiovisuele ondersteuning om externe deelnemers via TEAMS toe te laten.

Aanbevelingen

Aanbeveling-1: Organisatie diagnostische fase

Het expertiseteam levertumoren heeft minimaal eenmaal per week een multidisciplinair overleg (MDO). In het SONCOS normeringsrapport wordt per tumortype ingegaan op de invulling van het MDO en welke personen aan het MDO moeten deelnemen (SONCOS, 2023).

Hieruit volgt een behandeladvies wat met de patiënt, huisarts en verwijzend specialist gedeeld wordt. Volgens de principes van samen beslissen & informed consent, wordt het behandelvoorstel omgezet in een behandeldoel (KNMG, 2022). De bevindingen worden naar de huisarts en de verwijzer teruggekoppeld en vastgelegd in het medisch dossier. De bespreking wordt genotuleerd.

Stem diagnostiek en behandeling voor een patiënt met voor een maligniteit verdachte levertumor (HCC) af in een multidisciplinair overleg (MDO). Bij dit MDO dient deskundigheid voor diagnostiek en behandeling aanwezig te zijn, zoals in SONCOS normeringsdocument 2023, bij voorkeur aangevuld met:

- Radiotherapeut*
- Verpleegkundig specialist
- Nucleair geneeskundige*
- Patholoog*
- Internist-Endocrinoloog*

*op afroep bij casuïstiek ten behoeve van het betreffend specialisme.

Deel de uitslag van deze MDO bespreking zo spoedig mogelijk met belanghebbenden waarbij de patiënt ten eerste wordt geïnformeerd.

Bij voorkeur is dit traject vastgelegd in een zorgpad.

Literatuur

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Bijlagen bij module 12.1

Indicatoren
Bij deze module worden geen indicatoren opgeleverd.

Evidencetabellen
Niet van toepassing.

Exclusietabel
Niet van toepassing.

Zoekverantwoording
Niet van toepassing.

Module 12.2 Organisatie behandelfase

Uitgangsvraag

Wat is de optimale informatievoorziening rondom de behandeling van een patiënt met een hepatocellulair carcinoom?

Inleiding

Het is van belang om patiënten uitgebreid voor te lichten over alle facetten van lokale of systemische behandeling. Hierbij wordt gedacht aan mondelinge voorlichting, als ook folders en websites.

Zoeken en selecteren

Er is voor deze vraag geen systematische literatuuranalyse uitgevoerd. De aanbevelingen zijn gebaseerd op expert opinion van de expertisegroep, waar mogelijk onderbouwd met literatuur die door de expertisegroep leden is aangedragen.

Overwegingen

De keuze van het aangaan van een behandeling wordt bepaald door de patiënt die volledig geïnformeerd is over de voordelen (overlevingswinst) en de nadelen (morbiditeit, mortaliteit) van de voorgestelde behandeling, bij voorkeur in combinatie met schriftelijke en/of internetinformatie. De leeftijd van de patiënt, het stadium van de leverziekte en de algemene cardiopulmonale conditie en WHO-classificatie worden bij de overwegingen betrokken. De leverfunctie (Child-pugh) zal worden bepaald en bij eventuele beperkingen kan dit een rol spelen op de effecten van de behandeling. In geval van virale hepatitis is er aandacht voor zo mogelijk antivirale behandeling van de patiënt en screening en vaccinatie van de gezinsleden (RIVM, 2023). Voorlichting binnen een multidisciplinaire setting moet eenduidig worden gegeven, zodat iedere professional weet wanneer welke informatie aan de patiënt gegeven wordt en wie hiervoor verantwoordelijk is. Hierbij kan gedacht worden aan folders van de Maag-Lever-Darm stichting of informatieve websites. Het is van belang patiënten te wijzen op gezond beweeg- en voedingsgedrag, maar ook op risicofactoren die gezondheidsproblemen kunnen veroorzaken of verergeren (roken, overgewicht, alcohol gebruik) (Fernández, 2022).

<u>Waarden en voorkeuren van patiënten</u>

Samen beslissen over de behandel mogelijkheden of behandeling speelt een belangrijke rol. Goede voorlichting en informatievoorziening is hierbij essentieel voor de patiënt om een goede keuze te maken. De werkgroep adviseert daarom ook om voorlichting over de voor- en nadelen van een behandeling herhaaldelijk te bespreken en eventueel te ondersteunen met schriftelijke informatie. Ook moet aan de patiënt duidelijk worden gemaakt hoe de contactmomenten zijn ingericht. Dit kan opgenomen worden in een zorgpad.

Aanbevelingen

Aanbeveling-1: Organisatie behandelfase

<u>Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies</u>

Bespreek de voor- en nadelen van de behandelmogelijkheid of -mogelijkheden met de patiënt en richt daarbij de informatievoorziening op de volgende manier in zodat:

- Adequaat mondeling voorlichting gegeven wordt.
- Voorlichting gegeven wordt die op de fase van behandeling en de patient (en eventuele familie en naasten) toegesneden is.

- De (mondelinge) voorlichting met schriftelijke informatie of een website wordt ondersteund.
- Controleer bij de patiënt of de informatie is begrepen.

Literatuur

Fernández T, Viñuela M, Vidal C, Barrera F. Lifestyle changes in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis. PLoS One. 2022 Feb 17;17(2):e0263931. doi: 10.1371/journal.pone.0263931. PMID: 35176096; PMCID: PMC8853532.

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Bijlagen bij hoofdstuk 12.2

Indicatoren
Er worden geen indicatoren opgeleverd bij deze module.

Evidencetabellen
Niet van toepassing.

Exclusietabel
Niet van toepassing.

Zoekverantwoording
Niet van toepassing.

Module 12.3 Organisatie nazorg

Uitgangsvraag

Wat is de optimale organisatie van nazorg bij een patiënt met hepatocellulair carcinoom?

Inleiding

Het is voor zowel de patiënt als de behandelaars van belang dat er heldere communicatie is over de follow-up en nazorg. Per brief wordt gecommuniceerd, welke zorgverlener aanspreekpunt is aan patiënt en huisarts en verwijzer.

Zoeken en selecteren

Er is voor deze vraag geen systematische literatuuranalyse uitgevoerd. De aanbevelingen zijn gebaseerd op expert opinion van de expertisegroep, waar mogelijk onderbouwd met literatuur die door de expertisegroep leden is aangedragen.

Overwegingen

In iedere fase van de behandeling en het nazorgtraject moet het voor de patiënt, de huisarts en alle behandelaars duidelijk zijn wie de hoofdbehandelaar is, wie de nazorg coördineert, en wie het aanspreekpunt is. Welke zorgverlener dat is, kan in het multidisciplinair team afgesproken worden.

Er kan bijvoorbeeld voor een volgende opzet gekozen worden:

1. Patiënten die alleen chirurgisch zijn behandeld, worden gevolgd door de chirurg of een verpleegkundig specialist.
2. Patiënten die radiotherapie hebben gehad worden ofwel alleen door de chirurg gevolgd, ofwel alleen door de radiotherapeut-oncoloog (of door een verpleegkundig specialist).
3. Patiënten die systemische antitumorale behandeling krijgen of hebben gekregen worden gecontroleerd door de medisch oncoloog of een verpleegkundig specialist.
4. Patiënten met een HCC, cirrose, ascites of antivirale behandeling worden door de MDL- arts vervolgd.
5.

Nazorg interventies

Met name in het eerste jaar moet aandacht zijn voor psychosociale begeleiding.

Werkhervatting dient bespreekbaar te worden gemaakt en te worden gestimuleerd. Daarnaast dienen artsen en verpleegkundig specialisten op de hoogte te zijn van verwijsmogelijkheden voor psycho-oncologische zorg, sociale steungroepen/lotgenotencontact en revalidatieprogramma's.

Duur en afronding van nazorg

De follow-up na behandeling van het HCC is á drie maanden. De werkgroep adviseert daarna een 6-maandelijkse controle. De duur van de nazorg in het ziekenhuis dient in overleg tussen arts en patiënt te worden bepaald (zie module 6.2). Factoren zoals leeftijd, WHO-classificatie en persoonlijke omstandigheden dienen daarbij in overweging genomen te worden. De keuze voor de duur kan niet worden gemaakt zonder invulling te geven aan primaire aspecten van nazorg, zoals voorlichting en zorg voor de patiënt. Bij afronding van de nazorg in het ziekenhuis dient afgesproken te worden wie de contactpersoon blijft, dit moet schriftelijk gecommuniceerd worden aan de huisarts en andere betrokken partijen.

Aanbevelingen

Aanbeveling-1: Organisatie nazorgfase

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

Schrijf als medisch of verpleegkundig specialist voor elke patiënt een brief in begrijpelijke taal die ter beschikking komt van de patiënt, de huisarts en andere betrokken partijen bij afronding van behandeling en de follow-up.

Het nazorgplan vastgelegd in een ontslagbrief (overdracht) wordt ingezet, tenminste op de volgende momenten:

- Bij ontslag uit het ziekenhuis.
- Bij de afronding van de initiële kankerbehandeling.
- Bij veranderingen in de medische en/of psychosociale situatie van de patiënt.

In de ontslagbrief dienen tenminste de volgende zaken vermeld te worden:

- Diagnose.
- Behandeling.
- Alarmsymptomen.
- Contactgegevens contactpersoon van behandelcentrum of ziekenhuis.

5

Bijlagen bij hoofdstuk 12.3

Indicatoren
Er worden geen indicatoren opgeleverd bij deze module.

Evidencetabellen
Niet van toepassing.

Exclusietabel
Niet van toepassing.

Zoekverantwoording
Niet van toepassing.