Literaturrecherchen und Evidenztabellen für die Version 4 der S3-Leitlinie Diagnostik und Therapie des Hepatozellulären Karzinoms und biliärer Karzinome

Inhaltsverzeichnis

1. Methodisches Vorgehen

1.1. Leitlinienrecherche

In der aktuellen Version wurde keine Leitlinienrecherche und Leitlinienadaptation durchgeführt.

1.2. Systematische Literaturrecherche

1.2.1. Formulierung von Schlüsselfragen

Es handelt sich um die Aktualisierung der S3- Leitlinie „Hepatozelluläres Karzinom, Diagnostik und Therapie“ vom 01.07.2021 (AWMF-Registernummer 032 - 053OL).
Es wurden fünf Recherchen durchgeführt, davon drei aktualisierte Fragestellungen und zwei neue Fragestellungen.
Die Auflistung der Schlüsselfragen mit genauer Beschreibung des PICO-Schemas für die de-novo Fragestellungen finden sich im Kapitel 2.

1.2.2. Durchführung der Recherche

Die systematische Literaturrecherche wurde in der Medline Datenbank über die PubMed Suchoberfläche https://pubmed.ncbi.nlm.nih.gov/ durchgeführt. Zusätzlich erfolgten Recherchen in der Cochrane library und Cochrane Central Datenbanken über die Cochrane Suchoberfläche https://www.cochranelibrary.com/.
Die Suchen wurden zwischen dem 12.12.2022 und dem 13.12.2022 durchgeführt, jedoch wurde nur Literatur berücksichtigt, die bis zum 31.10.2022 publiziert wurde.
Die relevanten Publikationszeiträume unterscheiden sich allerdings zwischen den einzelnen Fragestellungen. Genauere Informationen hierzu finden sich im unter 2.21 Ausschlussgründe bzw. im Kapitel 2..
Es wurden 2684 Suchtreffer in Medline und 1835 Suchtreffer in der Cochrane-Library und Cochrane Central erzielt. Die Suchtreffer wurden kombiniert und die Duplikate wurden entfernt.
In Summe verblieben 4197 Literaturstellen, die über die Recherche identifiziert wurden. Die Ergebnisse der Suchen zu den einzelnen Datenbanken sind in Tabelle 1 aufgelistet. Die detaillierten Darstellungen der Recherchen sind im Kapitel 2. zur jeweiligen Schlüsselfrage dargestellt.

Tabelle 1 Ergebnisse der Literaturrecherche nach Kapitel und Datenbank

	PubMed	Cochrane Library	Cochrane Central	Kombiniert ohne Duplikate
HCC-Diagnostik	952	9	669	**1459**
HCC 20	702	0	60	**753**
CCA 15	69	1	88	**138**
Mischtumore	529	3	645	**1119**
Bestrahlung	432	2	358	**728**
	2684	**15**	**1820**	**4197**

1.3. Auswahl der Evidenz

Die Literaturarbeit wurde über das Leitlinienportal der Clinical Guideline Services GmbH (CGS) durchgeführt. Die in den Suchen identifizierten Literaturstellen wurden nach dem Deduplizieren als Literatursammlungen für jede PICO-Frage im Leitlinienportal (https://www.guideline-service.de) hinterlegt.
Die Literatursammlungen waren der Leitliniengruppe zu jedem Zeitpunkt zur Einsicht verfügbar. Die Auswahl der Literatur erfolgte durch Mitglieder des Koordinationsteams bzw. der Arbeitsgruppen.

1.3.1. Ein- und Ausschlussgründe

Folgende Ein- und Ausschlussgründe wurden für die Recherche und Auswahl der Evidenz festgelegt:

- Deutsche und englische Veröffentlichungen
- Probandenstudien (keine Tierversuche)
- Veröffentlichungszeitraum
    - zwischen 01/07/2021 und 31.10.2022 für die Aktualisierungs-recherchen zum hepatozellulären Karzinom und Cholangiokarzinom (HCC 20, CCA 15)
    - zwischen 01/01/2019 und 31.10.2022 für die neuen Fragestellungen zur Diagnostik des hepatozellulären Karzinoms (HCC-Diagnostik) und der Bestrahlung des hepatozellulären Karzinoms (Bestrahlung)

- zwischen 01/01/2015 und 31.10.2022 für die neue Fragestellung zu den Mischtumoren des Fibrolamellären hepatozellulären Karzinoms bzw. d Cholangiokarzinoms (Mischtumore)

Generelle Ausschlussgründe wurden ebenfalls zur Auswahl herangezogen:

- Doppelpublikation bzw. aktuellere Version vorhanden
- Primärstudie ist bereits in einer Übersichtsarbeit enthalten
- Kein Volltext verfügbar (bzw. Studien-Protokoll, Abstract)
- Überlappende Übersichtsarbeiten
- Nicht die gesuchte Population für die Fragestellung
- Nicht die gesuchte Intervention für die Fragestellung
- Nicht die gesuchten Outcomes für die Fragestellung
- Anderer Publikationstyp (Editorial, Fallbericht, Brief etc.)

1.3.2. Screening

Die Auswahl der Evidenz erfolgte durch ein mehrstufiges Screening im Leitlinienportal (https://www.guideline-service.de). Im ersten Schritt, dem Titel-Abstract Screening wurden die Suchtreffer anhand der Ein- und Ausschlussgründe auf potenzielle Relevanz gesichtet. Die Auswahl wurde von den Mitgliedern der Leitlinienkoordination getroffen und selbst im Leitlinienportal durchgeführt.
Von den von Duplikaten bereinigten 5895 Suchtreffern wurden 71 als potenziell relevant eingeordnet. Alle im Titel-Abstract als relevant für die jeweilige Fragestellung identifizierten Artikel wurden daraufhin als Volltext akquiriert.

Im zweiten Schritt des Screenings wurden die Volltexte der ausgewählten Publikationen auf die Erfüllung der o.g. Ausschlüssgründe überprüft. Es wurden 22 relevante Literaturstellen identifiziert. Die Auswahl wurde von den Mitgliedern der Arbeitsgruppen getroffen und selbst im Leitlinienportal durchgeführt. Im Anschluss wurden die relevanten Literaturstellen der Evidenzbewertung zugeführt.
Die Teilschritte des Screenings sind im Kapitel 2. zur jeweiligen Recherche grafisch als PRISMA Flussdiagram dargestellt.

1.3.3. Literatur aus Handsuche

Es wurde keine Literatur aus Handsuchen nachnominiert.
Allerdings wurden bei der Erstellung der PICO-Fragestellungen zu jeder Fragestellung eine

Liste mit Literatur durch die Leitliniengruppe zur Verfügung gestellt, welche erwartungsgemäß, die jeweilige Fragestellung beantworten soll. Diese wurden verwendet, um die Suchbegriffe für die neuen Suchen zu erstellen.

1.4. BewertungBewertung der Evidenz

Die Literaturbewertung wurde nach der Evidenzklassifizierung des *Oxford Centre for Evidence-Based Medicine 2011*[1] (Tabelle 2) für Interventions- diagnostische und prognostische Studien durchgeführt. Die methodische Qualität der Literaturstelle wurde mit Hilfe von Checklisten überprüft und die gefundenen Mängel im „Notes“ Bereich der Evidenztabellen festgehalten. Als Checklisten wurden je nach Studientyp die folgenden Checklisten genutzt:

- AMSTAR II für Übersichtsarbeiten[2],
- Cochrane Risk of bias tool[3] 1 für randomisierte kontrollierte Studien bzw.
- Newcastle-Ottawa Scale[4] für nicht-randomisierte Studien (Kohorten- und Fall-Kontroll Studien).

Studien mit bedeutenden methodischen Schwächen und/ oder bedeutsamer Heterogenität wurden um eine Note abgewertet. Eine entsprechende detaillierte Begründung findet sich in der Evidenztabelle im Feld „Notes“.
Nach der Bewertung der Literaturstellen wurden die Literaturstellen der jeweils passenden Schlüsselfrage zugeordnet.

Aus allen eingeschlossenen Literaturstellen wurden im nächsten Schritt Daten extrahiert und in Form von Evidenztabellen zusammengefasst. Insgesamt wurden 20 Literaturstellen bewertet. Zwei Literaturstellen wurden von der Bewertung ausgenommen, da diese - von anderer Seite und - nach GRADE bewertet werden sollten.

1 OCEBM Levels of Evidence Working Group*. “The Oxford Levels of Evidence 2”. Oxford Centre for Evidence-Based Medicine. https://www.cebm.net/index.aspx?o=5653 * OCEBM Levels of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson (abgerufen am 05.03.2020).

2 Shea B J, Reeves B C, Wells G, Thuku M, Hamel C, Moran J et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both BMJ 2017; 358 :j4008 doi:10.1136/bmj.j4008

3 Higgins J P T, Altman D G, Gotzsche P C, Jüni P, Moher D, Oxman A D et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials BMJ 2011; 343 :d5928 doi:10.1136/bmj.d5928

4 Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses (2014) http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (abgerufen am 25.02.2022)

Tabelle 2: Evidenzklassifizierung nach Oxford 2011

Fragestellung	**Schritt 1** (Level 1*)	**Schritt 2** (Level 2*)	**Schritt 3** (Level 3*)	**Schritt 4** (Level 4*)	**Schritt 5** (Level 5*)
Wie häufig ist das Problem	Lokale und aktuelle randomisierte Proben aus Umfragen (oder Volkszählungen)	Systematische Reviews von Umfragen die eine Anpassung an die örtlichen Gegebenheiten ermöglichen**	Lokale Nicht-Zufalls Probe	Fall-Serie**	Nicht verfügbar
Ist der diagnostische oder Monitoring Test akkurat? (Diagnose)	Systematische Reviews von Querschnittsstudien mit konsistent applizierten Referenzstandard und Verblindung	Einzelne Querschnitts-Studien mit konsistent applizierten Referenzstandard und Verblindung	Nicht konsekutive Studien oder Studien ohne konsistent applizierten Referenzstandard**	Fall-Kontroll Studien, oder minderwertiger, nicht unabhängiger Referenz Standard**	Mechanismus-basierte Argumentation
Was wird ohne Therapie passieren? (Prognose)	Systematische Reviews von Inzeptions Kohorten Studien	Inzeptions Kohorten Studien	Kohorten Studien oder Kontrollarme von randomisierten Studien*	Fall Serien oder Fall-Kontroll Studien, oder minderwertiger prognostische Kohorten Studien	Nicht verfügbar
Hilft die Intervention? Behandlungsvorteil	Systematische Reviews von randomisierten Studien oder n=1 Studien	Randomisierte Studien oder Observationsstudien mit dramatischem Effekt	Nicht-randomisierte kontrollierte Kohorten/Follow-up Studien**	Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien	Mechanismus-basierte Argumentation
Was sind die häufigen Nachteile/ Schäden durch die Intervention? Behandlungsnachteil	Systematische Reviews von randomisierten Studien oder Nested Fall Kontroll Studien, n=1 Studien, oder	Randomisierte Studien oder (herausragende) Observationsstudien mit dramatischem Effekt	Nicht-randomisierte kontrollierte Kohorten / Follow-up Studien (Beobachtung nach Marktzulassung), -ausreichende Fallzahl	Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien	Mechanismus-basierte Argumentation

	Observationsstudien mit dramatischem Effekt		vorausgesetzt - um häufige Schäden auszuschließen (Für Langzeit Schäden muss die Nachfolgezeit ausreichend sein)		
Was sind die seltenen Nachteile/ Schäden durch die Intervention? Behandlungsnachteil	Systematische Reviews von randomisierten Studien oder n=1 Studien	Randomisierte Studien oder herausragende Observationsstudien mit dramatischem Effekt		Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien	Mechanismus-basierte Argumentation
Ist der (frühe Detektion) Test lohnenswert? (Screening)	Systematische Reviews von randomisierten Studien	Randomisierte Studien	Nicht-randomisierte kontrollierte Kohorten / Follow-up Studien**	Fall Serien oder Fall-Kontroll Studien, oder historische kontrollierte Studien	Mechanismus-basierte Argumentation

* Das Evidenzlevel kann herabgestuft werden auf Grund der Studienqualität, Ungenauigkeit, Indirektheit (Studien PICO passt nicht genau zur Frage PICO), Inkonsistenz zwischen Studien, oder weil die absolute Effektgröße sehr klein ist. Das Evidenzlevel kann hochgestuft werden, wenn der beobachtete Effekt groß oder sehr groß ist.

** Wie immer ist ein Systematisches Review generell besser als eine einzelne Studie

[1] Entwickelt von OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson
2011. Übersetzt und angepasst von CGS GmbH 2020.

1.5. Erstellung von Evidenztabellen

Aus allen eingeschlossenen Literaturstellen wurden nach der positiven Bewertung die wichtigsten Daten extrahiert. Diese sind je nach Studientyp unterschiedlich (Diagnostik, Intervention, Beobachtung, Übersichtsarbeit) beinhalten aber in jedem Falle eine Beschreibung der Population, Intervention/ Exposure, Endpunkte, Resultate inklusive Zahlenwerte, Konklusion der Autor*innen und einer Auflistung der bei der Durchsicht offenkundigen methodischen Mängel. Diese Daten sind in Form von Evidenztabellen geordnet und nach Studientyp im Leitlinienportal zusammengefasst.
Die Evidenztabellen sind in Kapitel 3 zu den jeweiligen PICO-Schlüsselfragen dargestellt. Ebenfalls wurden Inhaltsverzeichnisse zu den Evidenztabellen erstellt. Diese beinhalten eine Auflistung der Literaturstellen der zugeordneten Literatur, das Evidenzlevel und die Angabe des Studientypes.

2. Ergebnisse der Literaturrecherchen

2.1. HCC Diagnostik

Frage	Population	Intervention	Alternativmaß-nahme	Outcome	Priorität
HCC Diagnostik Welche Untersuchungsmethoden sollen bei Patienten mit V.a. HCC zur Sicherung der Diagnose angewendet werden?	Patienten mit Leberzirrhose und V.a. HCC	CT CEUS	MRT	Diagnostische Sensitivität und Spezifität nach histologischer Aufarbeitung	9
				Maximale Ausdehnung des Tumors	8

Einschlusskriterien	
Zielgruppe	Patienten mit Leberzirrhose und V.a. HCC
Publikationstyp	Randomisierte kontrollierte Studien (RCTs) oder systematische Übersicht mit/ohne Metaanalyse oder RCTs, im weiteren Verlauf Fall Kontrollstudie, Kohortenstudie
Sprachen	Deutsch oder Englisch
Suchzeitraum	01.01.2019-31.10.2022

Recherche in PubMed (12.12.2022)

Nr	Query	Hits
Population		
#1	**Carcinoma, Hepatocellular[Mesh]** OR HCC[tiab] OR Hepatom*[tiab] OR ((Carcinoma*[tiab] OR Cancer[tiab] OR cancers[tiab]) AND (hepatocellular[tiab] OR liver cell[tiab] OR adult liver[tiab]))	172.763
#2	(**Neoplasms[Mesh]** OR Neoplas*[tiab] OR Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab]) AND (hepatocellular[tiab] OR hepatic*[tiab] OR liver*[tiab] OR "**Liver"[Mesh**])	326.695
#3	**Liver Cirrhosis[Mesh]** OR ((liver[Mesh]) AND ("Fibrosis"[Mesh] OR cirr*[tiab] OR fibrosis[tiab]))	113.532

#4	#1 OR #2 OR #3	466.886
Intervention		
#5	**Tomography, X-Ray Computed[Mesh]** OR computer tomography[tiab] OR CT scan[tiab] OR X-Ray Computed Tomography[tiab] OR X-Ray Computer Assisted Tomography[tiab] OR X Ray Computer Assisted Tomography[tiab] OR Computerized Tomography, X-Ray[tiab] OR X-Ray Computerized Tomography[tiab] OR CT X Ray[tiab] OR CT X Rays[tiab] OR X Ray, CT[tiab] OR X Rays, CT[tiab] OR Tomodensitometry[tiab] OR Tomography, X Ray Computed[tiab] OR X Ray Tomography, Computed[tiab] OR X-Ray Tomography, Computed[tiab] OR Computed X-Ray Tomography[tiab] OR Tomographies, Computed X-Ray[tiab] OR Tomography, Computed X-Ray[tiab] OR Tomography, Xray Computed[tiab] OR Computed Tomography, Xray[tiab] OR Xray Computed Tomography[tiab] OR CAT Scan, X Ray[tiab] OR CAT Scan, X-Ray[tiab] OR CAT Scans, X-Ray[tiab] OR Scan, X-Ray CAT[tiab] OR Scans, X-Ray CAT[tiab] OR X-Ray CAT Scan[tiab] OR X-Ray CAT Scans[tiab] OR Tomography, Transmission Computed[tiab] OR Computed Tomography, Transmission[tiab] OR Transmission Computed Tomography[tiab] OR CT Scan, X-Ray[tiab] OR CT Scan, X Ray[tiab] OR CT Scans, X-Ray[tiab] OR Scan, X-Ray CT[tiab] OR Scans, X-Ray CT[tiab] OR X-Ray CT Scan[tiab] OR X-Ray CT Scans[tiab] OR Tomography, X-Ray Computerized[tiab] OR Tomography, X Ray Computerized[tiab] OR Computed Tomography, X-Ray[tiab] OR Computed Tomography, X Ray[tiab] OR X Ray Computerized Tomography[tiab] OR Computed X Ray Tomography[tiab] OR Tomography, X-Ray Computer Assisted[tiab] OR Tomography, X Ray Computer Assisted[tiab] OR Computerized Tomography, X Ray[tiab] OR Cine-CT[tiab] OR Cine CT[tiab] OR Electron Beam Computed Tomography[tiab] OR Electron Beam Tomography[tiab] OR Beam Tomography, Electron[tiab] OR Tomography, Electron Beam[tiab] OR Tomography, X-Ray Computerized Axial[tiab] OR Tomography, X Ray Computerized Axial[tiab] OR X-Ray Computerized Axial Tomography[tiab] OR X Ray Computerized Axial Tomography[tiab]	52.151
#6	**Ultrasonography[Mesh]** OR Ultrasonography[tiab] OR Diagnostic Ultrasound[tiab] OR Diagnostic Ultrasounds[tiab] OR Ultrasound, Diagnostic[tiab] OR Ultrasounds, Diagnostic[tiab] OR Ultrasound Imaging[tiab] OR Imaging, Ultrasound[tiab] OR Imagings, Ultrasound[tiab] OR Echotomography[tiab] OR Ultrasonic Imaging[tiab] OR Imaging, Ultrasonic[tiab] OR Sonography, Medical[tiab] OR Medical Sonography[tiab] OR Ultrasonographic Imaging[tiab] OR Imaging, Ultrasonographic[tiab] OR Imagings, Ultrasonographic[tiab] OR Ultrasonographic Imagings[tiab] OR Echography[tiab] OR Diagnosis, Ultrasonic[tiab] OR	578.951

	Diagnoses, Ultrasonic[tiab] OR Ultrasonic Diagnoses[tiab] OR Ultrasonic Diagnosis[tiab] OR Echotomography, Computer[tiab] OR Computer Echotomography[tiab] OR Tomography, Ultrasonic[tiab] OR Ultrasonic Tomography[tiab] OR CEUS[tiab]	
#7	**Magnetic Resonance Imaging[Mesh]** OR Magnetic Resonance Imaging[tiab] OR Imaging, Magnetic Resonance[tiab] OR NMR Imaging[tiab] OR Imaging, NMR[tiab] OR Zeugmatography[tiab] OR MR Tomography[tiab] OR NMR Tomography[tiab] OR Tomography, NMR[tiab] OR Steady-State Free Precession MRI[tiab] OR Steady State Free Precession MRI[tiab] OR Tomography, MR[tiab] OR Imaging, Chemical Shift[tiab] OR Chemical Shift Imagings[tiab] OR Imagings, Chemical Shift[tiab] OR Shift Imaging, Chemical[tiab] OR Shift Imagings, Chemical[tiab] OR Chemical Shift Imaging[tiab] OR Magnetic Resonance Image[tiab] OR Image, Magnetic Resonance[tiab] OR Magnetic Resonance Images[tiab] OR Resonance Image, Magnetic[tiab] OR Magnetization Transfer Contrast Imaging[tiab] OR MRI Scans[tiab] OR MRI Scan[tiab] OR Scan, MRI[tiab] OR Scans, MRI[tiab] OR Tomography, Proton Spin[tiab] OR Proton Spin Tomography[tiab] OR fMRI[tiab] OR MRI, Functional[tiab] OR Functional MRI[tiab] OR Functional MRIs[tiab] OR MRIs, Functional[tiab] OR Functional Magnetic Resonance Imaging[tiab] OR Magnetic Resonance Imaging, Functional[tiab] OR Spin Echo Imaging[tiab] OR Echo Imaging, Spin[tiab] OR Echo Imagings, Spin[tiab] OR Imaging, Spin Echo[tiab] OR Imagings, Spin Echo[tiab] OR Spin Echo Imagings[tiab]	647.421
#8	#5 OR #6 OR #7	1.561.264
#9	#4 AND #8	54.398
Filter		
#10	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR	802.839

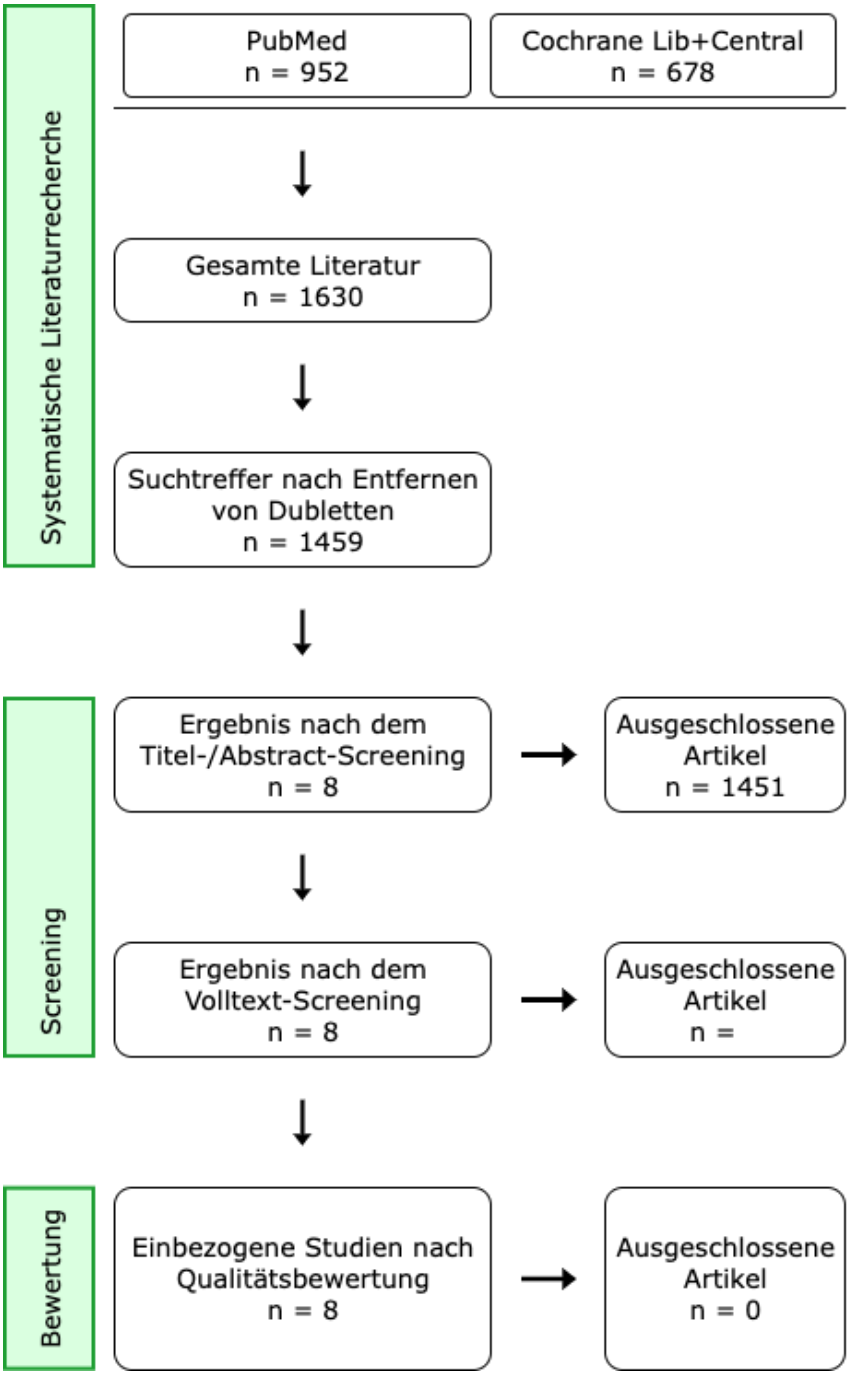
	metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	
#11	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.675.171
#12	#10 OR #11	2.311.324
#13	animals[mh] NOT humans[mh]	5.070.413
#14	#12 NOT #13	2.269.586
#15	#9 AND #14	4.257
#16	**Publication date from 01/01/2019 to 31.10.2022, English and German articles, Abstract available**	**952**

Recherche in der Cochrane Library (12.12.202)

ID	Search	Hits
#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	2055
#2	(Carcinoma, Hepatocellular OR hepatocellular carcinoma OR HCC OR Hepatom* OR ((Carcinoma* OR Cancer OR cancers) AND (hepatocellular OR liver cell OR adult liver))):ti,ab,kw	12570

#3	MeSH descriptor: [Neoplasms] explode all trees	90536
#4	(Neoplas* OR Tumor OR Tumors OR Cancer* OR Malignanc* OR carcinom):ti,ab,kw	241714
#5	#3 OR #4	252906
#6	MeSH descriptor: [Liver] explode all trees	3504
#7	(hepatocellular OR hepatic* OR liver*):ti,ab,kw	68318
#8	#6 OR #7	68340
#9	#5 AND #8	20215
#10	MeSH descriptor: [Liver Cirrhosis] explode all trees	3228
#11	MeSH descriptor: [Liver] explode all trees	3504
#12	(liver OR hepat*):ti,ab,kw	83991
#13	#11 OR #12	84010
#14	MeSH descriptor: [Fibrosis] explode all trees	6562
#15	(cirrh* OR fibros* OR fibrot*):ti,ab,kw	26648
#16	#14 OR #15	28394
#17	#13 AND #16	13095
#18	#1 OR #2 OR #9 OR #10 OR #17	32755
#19	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees	5629
#20	(Tomography, X-Ray Computed OR computer tomography OR CT scan OR X-Ray Computed Tomography OR X-Ray Computer Assisted Tomography OR X Ray Computer Assisted Tomography OR Computerized Tomography, X-Ray OR X-Ray Computerized Tomography OR CT X Ray OR CT X Rays OR X Ray, CT OR X Rays, CT OR Tomodensitometry OR Tomography, X Ray Computed OR X Ray Tomography, Computed OR X-Ray Tomography, Computed OR Computed X-Ray Tomography OR Tomographies, Computed X-Ray OR Tomography, Computed X-Ray OR Tomography, Xray Computed OR Computed Tomography, Xray OR Xray Computed Tomography OR CAT Scan, X Ray OR CAT Scan, X-Ray OR CAT Scans, X-Ray OR Scan, X-Ray CAT OR Scans, X-Ray CAT OR X-Ray CAT Scan OR X-Ray CAT Scans OR Tomography, Transmission Computed OR Computed Tomography, Transmission OR Transmission Computed Tomography OR CT Scan, X-Ray OR CT Scan, X Ray OR CT Scans, X-Ray OR Scan, X-Ray CT OR Scans, X-Ray CT OR X-Ray CT Scan OR X-Ray CT Scans OR Tomography, X-Ray Computerized OR Tomography, X Ray Computerized OR Computed Tomography, X-Ray OR Computed Tomography, X Ray OR X Ray Computerized Tomography OR Computed X Ray Tomography OR Tomography, X-Ray Computer Assisted OR Tomography, X Ray Computer Assisted OR Computerized Tomography, X Ray OR Cine-CT OR Cine CT OR Electron Beam Computed Tomography OR Electron Beam	21148

	Tomography OR Beam Tomography, Electron OR Tomography, Electron Beam OR Tomography, X-Ray Computerized Axial OR Tomography, X Ray Computerized Axial OR X-Ray Computerized Axial Tomography OR X Ray Computerized Axial Tomography):ti,ab,kw	
#21	MeSH descriptor: [Ultrasonography] explode all trees	14980
#22	(Ultrasonography OR Diagnostic Ultrasound OR Diagnostic Ultrasounds OR Ultrasound, Diagnostic OR Ultrasounds, Diagnostic OR Ultrasound Imaging OR Imaging, Ultrasound OR Imagings, Ultrasound OR Echotomography OR Ultrasonic Imaging OR Imaging, Ultrasonic OR Sonography, Medical OR Medical Sonography OR Ultrasonographic Imaging OR Imaging, Ultrasonographic OR Imagings, Ultrasonographic OR Ultrasonographic Imagings OR Echography OR Diagnosis, Ultrasonic OR Diagnoses, Ultrasonic OR Ultrasonic Diagnoses OR Ultrasonic Diagnosis OR Echotomography, Computer OR Computer Echotomography OR Tomography, Ultrasonic OR Ultrasonic Tomography OR CEUS):ti,ab,kw	27469
#23	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees	9034
#24	(Magnetic Resonance Imaging OR Magnetic Resonance Imaging OR Imaging, Magnetic Resonance OR NMR Imaging OR Imaging, NMR OR Zeugmatography OR MR Tomography OR NMR Tomography OR Tomography, NMR OR Steady-State Free Precession MRI OR Steady State Free Precession MRI OR Tomography, MR OR Imaging, Chemical Shift OR Chemical Shift Imagings OR Imagings, Chemical Shift OR Shift Imaging, Chemical OR Shift Imagings, Chemical OR Chemical Shift Imaging OR Magnetic Resonance Image OR Image, Magnetic Resonance OR Magnetic Resonance Images OR Resonance Image, Magnetic OR Magnetization Transfer Contrast Imaging OR MRI Scans OR MRI Scan OR Scan, MRI OR Scans, MRI OR Tomography, Proton Spin OR Proton Spin Tomography OR fMRI OR MRI, Functional OR Functional MRI OR Functional MRIs OR MRIs, Functional OR Functional Magnetic Resonance Imaging OR Magnetic Resonance Imaging, Functional OR Spin Echo Imaging OR Echo Imaging, Spin OR Echo Imagings, Spin OR Imaging, Spin Echo OR Imagings, Spin Echo OR Spin Echo Imagings):ti,ab,kw	35028
#25	#19 OR #20 OR #21 OR #22 OR #23 OR #24	81964
#26	#18 AND #25	3303
#27	#26 with Cochrane Library publication date Between Jan 2019 and Oct 2022, in Cochrane Reviews	9
#28	#26 with Publication Year from 2019 to 2022, in Trials	1047
#29	#28 NOT (clinicaltrials.gov OR CT.gov OR ICTRP)	669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Einbezogene Studien nach Qualitätsbewertung
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2.2. HCC 20 Systemtherapie

Frage	Population	Intervention	Alternativmaßnahme	Outcome	Priorität
HCC 20 Systemtherapie Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem HCC?	Patienten mit fortgeschrittenem HCC	Atezolizumab, Bevacizumab Durvalumab, Tremelimumab Sorafenib Lenvatinib Regorafenib Cabozantinib Ramucirumab PD1-Inhibitoren CTLA4-Inhibitoren	Keine Therapie oder gegen Sorafenib/ andere Therapien	Overall survival	9
				Time to Progression oder Progression free survival	9
				Adverse Events	7
				Quality of life	7

Einschlusskriterien	Allgemeine Einschlusskritieren
Zielgruppe	Patienten mit hepatozellulärem Karzinom, nicht resektabel, keine lokoregionäre Therapie
Publikationstyp	Randomisierte kontrollierte Studien (RCTs) oder systematische Übersicht mit/ohne Metaanalyse oder RCTs, im weiteren Verlauf Fall Kontrollstudie, Kohortenstudie
Sprachen	Deutsch oder Englisch
Suchzeitraum	01.07.2021-31.10.2022

Suche in PubMed (12.12.2022)

Nr	Query	Hits
Population		
#1	**Carcinoma, Hepatocellular[Mesh]** OR HCC[tiab] OR Hepatom*[tiab] OR ((Carcinoma*[tiab] OR Cancer[tiab] OR cancers[tiab]) AND (hepatocellular[tiab] OR liver cell[tiab] OR adult liver[tiab]))	172.763
#2	(**Neoplasms[Mesh]** OR Neoplas*[tiab] OR Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab]) AND (hepatocellular[tiab] OR hepatic*[tiab] OR liver*[tiab] OR "**Liver"[Mesh**])	326.695

#3	**Liver Cirrhosis[Mesh]** OR ((liver[Mesh]) AND ("Fibrosis"[Mesh] OR cirr*[tiab] OR fibrosis[tiab]))	113.532
#4	#1 OR #2 OR #3	466.886
Intervention		
#5	**atezolizumab [Supplementary Concept]** OR atezolizumab[tiab] OR anti-PDL1[tiab] OR MPDL3280A[tiab] OR MPDL-3280A[tiab] OR Tecentriq[tiab] OR RG7446[tiab] OR RG-7446[tiab]	2.685
#6	**Bevacizumab[Mesh]** OR Bevacizumab[tiab] OR Mvasi[tiab] OR Avastin[tiab]	21.796
#7	**durvalumab [Supplementary Concept]** OR durvalumab[tiab] OR MEDI4736[tiab] OR MEDI-4736[tiab] OR Imfinzi[tiab]	1.270
#8	**tremelimumab [Supplementary Concept]** OR tremelimumab[tiab] OR ticilimumab[tiab] OR CP 675[tiab] OR CP675 cpd[tiab] OR CP-675[tiab] OR CP-675,206[tiab] OR CP-675206[tiab] OR CP675206[tiab] OR CP 675206[tiab]	450
#9	**Sorafenib[Mesh]** OR Sorafenib[tiab] OR Nexavar[tiab] OR BAY 43-9006[tiab] OR BAY 43 9006[tiab] OR BAY 439006[tiab] OR Sorafenib N-Oxide[tiab] OR Sorafenib N Oxide[tiab] OR BAY-673472[tiab] OR BAY 673472[tiab] OR BAY 545-9085[tiab] OR BAY 545 9085[tiab] OR BAY 5459085[tiab] OR BAY-545-9085[tiab] OR BAY5459085[tiab]	11.117
#10	**"lenvatinib" [Supplementary Concept]** OR Lenvatinib[tiab] OR E 7080[tiab] OR E-7080[tiab] OR Lenvima[tiab]	1.710
#11	**regorafenib [Supplementary Concept]** OR Regorafenib[tiab] OR Stivarga[tiab] OR BAY 73-4506[tiab] OR BAY73-4506[tiab] OR BAY-73-4506[tiab]	1.724
#12	**cabozantinib [Supplementary Concept]** OR Cabozantinib[tiab] OR Cometriq[tiab] OR XL 184[tiab] OR XL184 cpd[tiab] OR XL-184[tiab] OR BMS 907351[tiab] OR BMS907351[tiab] OR BMS-907351[tiab]	1.421
#13	**ramucirumab [Supplementary Concept]** OR Ramucirumab[tiab] OR Cyramza[tiab] OR IMC 1121B[tiab] OR IMC1121B[tiab] OR IMC-1121B[tiab]	1.155
#14	**("Programmed Cell Death 1 Receptor"[Mesh]** OR PD-1[tiab] OR PD 1[tiab] OR programmed cell death protein 1[tiab] OR CD279 Antigen[tiab] OR Antigen, CD279[tiab]) AND (inibitor*[tiab] OR antibod*[tiab] OR antagonist[tiab]) OR PD-L1[tiab] OR PD L1[tiab]	26.339
#15	**Nivolumab[Mesh]** OR Opdivo[tiab] OR ONO-4538[tiab] OR ONO 4538[tiab] OR ONO4538[tiab] OR MDX-1106[tiab] OR MDX 1106[tiab] OR MDX1106[tiab] OR BMS-936558[tiab] OR BMS 936558[tiab] OR BMS936558[tiab]	4.726
#16	**pembrolizumab [Supplementary Concept]** OR Pembrolizumab[tiab] OR lambrolizumab[tiab] OR Keytruda[tiab] OR MK-3475[tiab]	7.833

#17	(**CTLA-4 Antigen[Mesh]** OR CTLA-4[tiab] OR CD152[tiab] OR Cytotoxic T-Lymphocyte-Associated Antigen 4[tiab] OR Cytotoxic T Lymphocyte Associated Antigen 4[tiab] OR Cytotoxic T-Lymphocyte Antigen 4[tiab] OR Cytotoxic T Lymphocyte Antigen 4[tiab]) AND (inibitor*[tiab] OR antibod*[tiab] OR antagonist[tiab])	3.908
#18	**Ipilimumab[Mesh]** OR Ipilimumab*[tiab] OR Yervoy[tiab] OR MDX 010[tiab] OR MDX010[tiab] OR MDX-010[tiab] OR MDX-CTLA-4[tiab] OR MDX CTLA 4[tiab]	5.104
#19	**Immunotherapy, Active[Mesh]** OR Immunotherap*[tiab] OR (immun*[tiab] AND therap*[tiab])	696.271
#20	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	743.490
#21	#4 AND #20	32.807
Filter		
#22	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	802.839
#23	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR	1.675.171

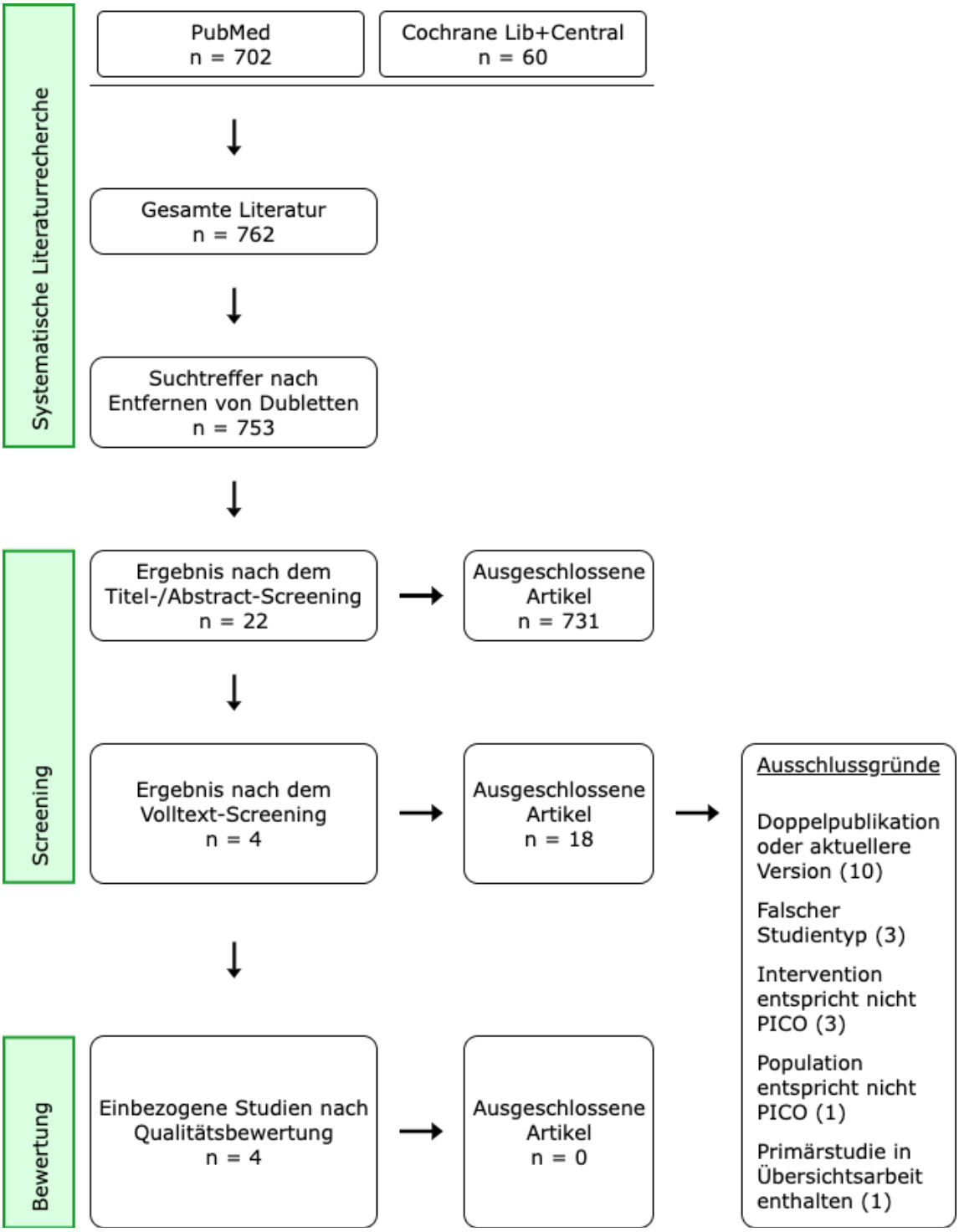
	doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab])	
#24	#22 OR #23	2.311.324
#25	animals[mh] NOT humans[mh]	5.070.413
#26	#24 NOT #25	2.269.586
#27	#21 AND #26	4.347
#28	**Publication date from 01/07/2021 to date 31.10.2022, English and German articles, Abstract available**	**702**

Recherche in der Cochrane Library (12.12.2022)

ID	Search	Hits
#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	2055
#2	(Carcinoma, Hepatocellular OR hepatocellular carcinoma OR HCC OR Hepatom* OR ((Carcinoma* OR Cancer OR cancers) AND (hepatocellular OR liver cell OR adult liver))):ti,ab,kw	12570
#3	MeSH descriptor: [Neoplasms] explode all trees	##########
#4	(Neoplas* OR Tumor OR Tumors OR Cancer* OR Malignanc* OR carcinom):ti,ab,kw	241714
#5	#3 OR #4	252906
#6	MeSH descriptor: [Liver] explode all trees	3504
#7	(hepatocellular OR hepatic* OR liver*):ti,ab,kw	68318
#8	#6 OR #7	68340
#9	#5 AND #8	20215
#10	MeSH descriptor: [Liver Cirrhosis] explode all trees	3228
#11	MeSH descriptor: [Liver] explode all trees	3504
#12	(liver OR hepat*):ti,ab,kw	83991
#13	#11 OR #12	84010
#14	MeSH descriptor: [Fibrosis] explode all trees	6562
#15	(cirrh* OR fibros* OR fibrot*):ti,ab,kw	26648
#16	#14 OR #15	28394
#17	#13 AND #16	13095
#18	#1 OR #2 OR #9 OR #10 OR #17	32755

#19	(atezolizumabOR atezolizumab OR anti-PDL1 OR MPDL3280A OR MPDL-3280A OR Tecentriq OR RG7446 OR RG-7446):ti,ab,kw	212
#20	MeSH descriptor: [Bevacizumab] explode all trees	2267
#21	(Bevacizumab OR Mvasi OR Avastin):ti,ab,kw	7207
#22	(durvalumab OR MEDI4736 OR MEDI-4736 OR Imfinzi):ti,ab,kw	960
#23	(tremelimumab OR ticilimumab OR CP 675 OR CP675 cpd OR CP-675 OR CP-675,206 OR CP-675206 OR CP675206 OR CP 675206):ti,ab,kw	391
#24	MeSH descriptor: [Sorafenib] explode all trees	540
#25	(Sorafenib OR Nexavar OR BAY 439006 OR Sorafenib N Oxide OR BAY 67347 OR BAY 545 9085 OR BAY 5459085 OR BAY5459085):ti,ab,kw	2058
#26	(Lenvatinib OR E 7080 OR E-7080 OR Lenvima):ti,ab,kw	631
#27	(Regorafenib OR Stivarga):ti,ab,kw	618
#28	(Cabozantinib OR Cometriq OR XL 184 OR XL184 cpd OR XL-184 OR BMS 907351 OR BMS907351 OR BMS-907351):ti,ab,kw	478
#29	(Ramucirumab OR Cyramza OR IMC 1121B OR IMC1121B OR IMC-1121B):ti,ab,kw	612
#30	((Programmed Cell Death 1 Receptor OR PD-1 OR PD 1 OR programmed cell death protein 1 OR CD279 Antigen OR Antigen, CD279) AND (inibitor* OR antibod* OR antagonist) OR PD-L1 OR PD L1):ti,ab,kw	7010
#31	MeSH descriptor: [Nivolumab] explode all trees	615
#32	(Nivolumab OR Opdivo OR ONO-4538 OR ONO 4538 OR ONO4538 OR MDX-1106 OR MDX 1106 OR MDX1106 OR BMS-936558 OR BMS 936558 OR BMS936558):ti,ab,kw	2610
#33	(Pembrolizumab OR lambrolizumab OR Keytruda OR MK-3475):ti,ab,kw	2594
#34	MeSH descriptor: [CTLA-4 Antigen] explode all trees	52
#35	(CTLA-4 Antigen OR CTLA-4 OR CD152 OR Cytotoxic T-Lymphocyte-Associated Antigen 4 OR Cytotoxic T Lymphocyte Associated Antigen 4 OR Cytotoxic T-Lymphocyte Antigen 4 OR Cytotoxic T Lymphocyte Antigen 4):ti,ab,kw	830
#36	#34 OR #35	830
#37	(inibitor* OR antibod* OR antagonist):ti,ab,kw	75114

#38	#36 AND #37	376
#39	MeSH descriptor: [Ipilimumab] explode all trees	278
#40	(Ipilimumab* OR Yervoy OR MDX 010 OR MDX010 OR MDX-010 OR MDX-CTLA-4 OR MDX CTLA 4):ti,ab,kw	1667
#41	MeSH descriptor: [Immunotherapy, Active] explode all trees	3002
#42	(Immunotherap* OR (immun* AND therap*)):ti,ab,kw	88433
#43	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #38 OR #39 OR #40 OR #41 OR #42	104966
#44	#18 AND #43	5999
#45	#18 AND #32	275
#46	**#45 with Cochrane Library publication date Between Jul 2021 and Oct 2022, in Cochrane Reviews**	**0**
#47	#45 with Publication Year from 2021 to 2022, in Trials	72
#48	**#47 NOT (clinicaltrials.gov OR CT.gov OR ICTRP)**	**60**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Population entspricht nicht PICO (1)
Primärstudie in Übersichtsarbeit enthalten (1)
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2.3. CCA 15 Systemtherapie

Frage	Population	Intervention	Alternativmaßnahme	Outcome	Priorität
CCA 15 Systemtherapie Von welchen Systemtherapien profitieren Patienten mit fortgeschrittenem biliären Karzinom?	Intrahepatisches CCA Perihiläres CCA Distales CCA Gallenblasenkarzinom	Durvalumab FGFR-Inhibitoren Futibatinib Infigratinib Pemigatinib Gemcitabin Cisplatin Capecitabine Ivosidenib 5-FU Oxaliplatin Irinotecan Ramucirumab	Keine Therapie, andere Systemtherapie	Overall survival	9
				Time to Progression oder Progression free survival	9
				Adverse Events	7
				Quality of life	7

Einschlusskriterien	
Zielgruppe	Patienten mit biliärem Karzinom, nicht resektabel
Publikationstyp	Randomisierte kontrollierte Studien (RCTs) oder systematische Übersicht mit/ohne Metaanalyse oder RCTs, im weiteren Verlauf Fall Kontrollstudie, Kohortenstudie
Sprachen	Deutsch oder Englisch
Suchzeitraum	01.07.2021-31.10.2022

Suche in PubMed (06.07.2021)

Nr	Query	Hits
Population		
#1	**Cholangiocarcinoma[Mesh]** OR Cholangiocarcinoma*[tiab] OR Cholangiocellular Carcinoma[tiab] OR Carcinoma, Cholangiocellular[tiab] OR Carcinomas, Cholangiocellular[tiab] OR Cholangiocellular Carcinoma*[tiab]	19.552
#2	(**Neoplasms[Mesh]** OR Neoplas*[tiab] OR Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab] OR carcinom*[tiab]) AND (bile duct*[tiab] OR biliary tract[tiab] OR bile canaliculi[tiab] OR cholangio*[tiab])	38.935
#3	#1 OR #2	41.344

#4	((gallbladder[tiab] OR gall bladder[tiab] OR biliary tract[tiab]) AND (Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab] OR carcinom*[tiab])) OR **"Gallbladder Neoplasms"[Mesh]**	19.978
#5	#3 OR #4	52.792
Intervention		
#6	**durvalumab [Supplementary Concept]** OR durvalumab[tiab] OR MEDI4736[tiab] OR MEDI-4736[tiab] OR Imfinzi[tiab]	1.310
#7	(**Receptors, Fibroblast Growth Factor[Mesh]** OR FGFR[tiab] OR Receptors, FGF[tiab] OR Fibroblast Growth Factor Receptor[tiab] OR Fibroblast Growth Factor Receptors[tiab] OR FGF Receptor[tiab] OR Receptor, FGF[tiab] OR FGF Receptors[tiab] OR Heparin-Binding Growth Factor Receptor[tiab] OR Heparin Binding Growth Factor Receptor[tiab]) AND (inhibitor*[tiab] OR antagonist*[tiab])	3.904
#8	futibatinib [Supplementary Concept] OR futibatinib[tiab]	30
#9	infigratinib [Supplementary Concept] OR infigratinib[tiab] OR BGJ398[tiab] OR truseltiq[tiab]	224
#10	**"pemigatinib" [Supplementary Concept]** OR Pemigatinib[tiab] OR Pemazyre[tiab] OR INCB054828[tiab] OR INCB-054828[tiab]	102
#11	**gemcitabine [Supplementary Concept]** OR gemcitabin*[tiab] OR dFdCyd[tiab] OR LY 188011[tiab] OR LY-188011[tiab] OR Gemzar[tiab]	20.061
#12	**Cisplatin[Mesh]** OR cis-plat*[tiab] OR cis plat*[tiab] OR Platinum Diamminodichloride[tiab] OR Diamminodichloride, Platinum[tiab] OR Dichlorodiammineplatinum[tiab] OR cis-Diamminedichloroplatinum[tiab] OR cis Diamminedichloroplatinum[tiab] OR NSC-119875[tiab] OR Platino[tiab] OR Platinol[tiab] OR Biocisplatinum[tiab] OR Platidiam[tiab]	58.724
#13	**Capecitabine[Mesh]** OR capecitabin*[tiab]	8.495
#14	ivosidenib [Supplementary Concept] OR ivosidenib[tiab] OR AG-120[tiab] OR Tibsovo[tiab]	223
#15	**"Fluorouracil"[Mesh]** OR Fluorouracil[tiab] OR 5FU[tiab] OR 5-FU[tiab] OR 5-Fluorouracil[tiab] OR 5 Fluorouracil[tiab] OR Fluoruracil[tiab] OR Adrucil[tiab] OR Carac[tiab] OR Efudix[tiab] OR Fluoro-Uracile[tiab] OR Fluoro Uracile[tiab] OR Efudex[tiab] OR Fluoroplex[tiab] OR Flurodex[tiab] OR Fluorouracilo[tiab] OR Fluracedyl[tiab] OR Haemato-FU[tiab] OR Haemato FU[tiab] OR Neofluor[tiab] OR Onkofluor[tiab] OR Ribofluor[tiab] OR 5-Fluorouracil-Biosyn[tiab] OR 5 Fluorouracil Biosyn[tiab]	67.220
#16	**Oxaliplatin[Mesh]** OR Oxaliplatin[tiab] OR Oxaliplatine[tiab] OR Eloxatine[tiab] OR Eloxatin[tiab] OR ACT 078[tiab] OR ACT-078[tiab] OR ACT078[tiab]	14.592

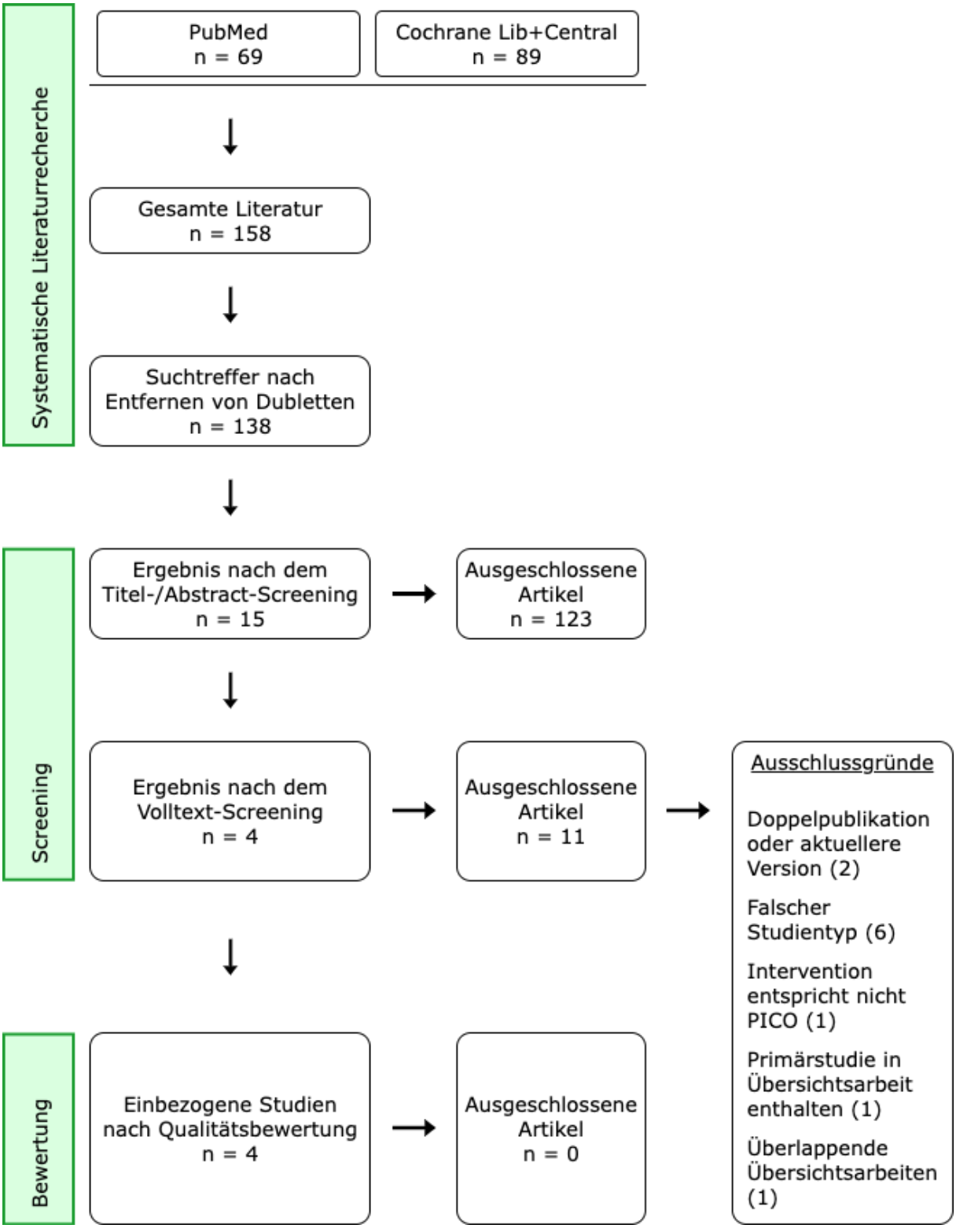
#17	**Irinotecan[Mesh]** OR Irinotecan[tiab] OR Camptothecin-11[tiab] OR Camptothecin 11[tiab] OR SN 38 11[tiab] OR SN-38-11[tiab] OR SN3811[tiab] OR SN 38[tiab] OR SN-38[tiab] OR NK012 Compound[tiab] OR CPT-11[tiab] OR CPT11[tiab] OR CPT 11[tiab] OR Camptosar[tiab]	9.047
#18	ramucirumab [Supplementary Concept] OR ramucirumab[tiab] OR LY3009806[tiab] OR Cyramza[tiab] OR IMC 1121B[tiab] OR IMC1121B[tiab] OR IMC-1121B[tiab] OR 1121B[tiab]	1.177
#19	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	140.411
#20	#5 AND #19	2.715
Filter		
#21	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	802.839
#22	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.675.171

#23	#21 OR #22	2.311.324
#24	animals[mh] NOT humans[mh]	5.070.413
#25	#23 NOT #24	2.269.586
#26	#20 AND #25	731
#27	Publication date from 01/07/2021 to date of search, English and German articles, Abstract available	**69**

Recherche in der Cochrane Library (12.12.2022)

ID	Search	Hits
#1	MeSH descriptor: [Cholangiocarcinoma] explode all trees	266
#2	(Cholangiocarcinoma* OR Cholangiocellular Carcinoma OR Carcinoma, Cholangiocellular OR Carcinomas, Cholangiocellular OR Cholangiocellular Carcinoma* OR CCA):ti,ab,kw	1283
#3	MeSH descriptor: [Neoplasms] explode all trees	90536
#4	(Neoplasms OR Neoplas* OR Tumor OR Tumors OR Cancer* OR Malignanc* OR carcinom*):ti,ab,kw	249130
#5	#3 OR #4	259510
#6	(bile duct* OR biliary tract OR bile canaliculi OR cholangio* OR gallbladder OR gall bladder OR biliary tract):ti,ab,kw	8869
#7	#5 AND #6	2828
#8	MeSH descriptor: [Gallbladder Neoplasms] explode all trees	97
#9	#1 OR #2 OR #7 OR #8	3273
#10	(durvalumab OR MEDI4736 OR MEDI-4736 OR Imfinzi):ti,ab,kw	960
#11	((Receptors, Fibroblast Growth Factor OR FGFR OR Receptors, FGF OR Fibroblast Growth Factor Receptor OR Fibroblast Growth Factor Receptors OR FGF Receptor OR Receptor, FGF OR FGF Receptors OR Heparin-Binding Growth Factor Receptor OR Heparin Binding Growth Factor Receptor) AND (inhibitor* OR antagonist*)):ti,ab,kw	354
#12	(futibatinib):ti,ab,kw	7
#13	(infigratinib OR BGJ398 OR truseltiq):ti,ab,kw	26
#14	(Pemigatinib OR Pemazyre OR INCB054828 OR INCB-054828):ti,ab,kw	12
#15	(gemcitabin* OR dFdCyd OR LY 188011 OR LY-188011 OR Gemzar):ti,ab,kw	6676
#16	MeSH descriptor: [Cisplatin] explode all trees	5328
#17	(Cisplatin OR cis-plat* OR cis plat* OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR	16202

	cis Diamminedichloroplatinum OR NSC-119875 OR Platino OR Platinol OR Biocisplatinum OR Platidiam):ti,ab,kw	
#18	MeSH descriptor: [Capecitabine] explode all trees	1422
#19	(capecitabin*):ti,ab,kw	4513
#20	(ivosidenib OR AG-120 OR Tibsovo):ti,ab,kw	64
#21	MeSH descriptor: [Fluorouracil] explode all trees	6537
#22	(Fluorouracil OR 5FU OR 5 Fluorouracil OR Fluoruracil OR Adrucil OR Carac OR Efudix OR Fluoro-Uracile OR Fluoro Uracile OR Efudex OR Fluoroplex OR Flurodex OR Fluorouracilo OR Fluracedyl OR Haemato-FU OR Haemato FU OR Neofluor OR Onkofluor OR Ribofluor OR 5 Fluorouracil Biosyn):ti,ab,kw	11645
#23	MeSH descriptor: [Oxaliplatin] explode all trees	1407
#24	(Oxaliplatin OR Oxaliplatine OR Eloxatine OR Eloxatin OR ACT 078 OR ACT-078 OR ACT078):ti,ab,kw	5379
#25	MeSH descriptor: [Irinotecan] explode all trees	989
#26	(Irinotecan OR Camptothecin OR SN3811 OR SN 38 OR SN-38 OR NK012 Compound OR CPT-11 OR CPT11 OR CPT 11 OR Camptosar):ti,ab,kw	4328
#27	(ramucirumab OR LY3009806 OR Cyramza OR IMC 1121B OR IMC1121B OR IMC-1121B OR 1121B):ti,ab,kw	612
#28	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	36526
#29	#9 AND #28	784
#30	#29 with Cochrane Library publication date Between Jul 2021 and Oct 2022, in Cochrane Reviews	1
#31	#29 with Publication Year from 2021 to 2022, in Trials	127
#32	#31 NOT (ct.gov OR ICTRP)	88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Cochrane Lib+Central
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Gesamte Literatur
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Doppelpublikation oder aktuellere Version (2)
Falscher Studientyp (6)
Intervention entspricht nicht PICO (1)
Primärstudie in Übersichtsarbeit enthalten (1)
Überlappende Übersichtsarbeiten (1)
Bewertung
Einbezogene Studien nach Qualitätsbewertung
n = 4
Ausgeschlossene Artikel
n = 0

2.4. Neue Frage Mischtumore/FL-HCC

Frage	Population	Intervention	Alternativmaßnahme	Outcome	Priorität
Systemtherapie Von welchen Systemtherapien profitieren Patienten mit einem Mischtumor oder fibrolamellären HCC?	Mischtumore (HCC/CCA) Fibrolamelläres HCC	Systemtherapie Letrozol Everolimus Immuntherapie Tyrosinkinaseinhibitor Platinbasierte Chemotherapie	Keine Therapie, andere Systemtherapie	Overall survival	8
				Time to Progression oder Progression free survival	9
				Adverse Events	7
				Ansprechrate (RECIST)	8

Einschlusskriterien	
Zielgruppe	Patienten mit biliärem Karzinom, nicht resektabel
Publikationstyp	Randomisierte kontrollierte Studien (RCTs) Fall-Kontrollstudie, Kohortenstudie
Sprachen	Deutsch oder Englisch
Suchzeitraum	01.01.2015-31.10.2022

Suche in PubMed (12.12.2022)

Nr	Query	Hits
Population		
#1	**Carcinoma, Hepatocellular[Mesh]** OR Carcinoma, Hepatocellular[tiab] OR Hepatocellular Carcinoma[tiab] OR HCC[tiab] OR Hepatom*[tiab] OR ((Carcinoma*[tiab] OR Cancer[tiab] OR cancers[tiab]) AND (hepatocellular[tiab] OR liver cell[tiab] OR adult liver[tiab]))	172.763
#2	**Cholangiocarcinoma[Mesh]** OR Cholangiocarcinoma*[tiab] OR CCA[tiab] OR Cholangiocellular Carcinoma[tiab] OR Carcinoma, Cholangiocellular[tiab] OR Carcinomas, Cholangiocellular[tiab] OR Cholangiocellular Carcinoma*[tiab]	27.643
#3	#1 OR #2	195.909
#4	combined[tiab] OR mixed[tiab]	1.359.009
#5	#3 AND #4	13.146

#6	combined HCC[tiab] OR combined CCA[tiab] OR mixed HCC[tiab] OR mixed CCA[tiab] OR cHCC-CCA[tiab] OR Fibrolamellar hepatocellular carcinoma [Supplementary Concept]	415
#7	#5 OR #6	13.313
Intervention		
#6	**systemic therap*[tiab]**	20.686
#7	**Letrozole[Mesh]** OR Letrozol*[tiab] OR CGS 20267[tiab] OR CGS-20267[tiab] OR CGS20267[tiab] OR Femara[tiab] OR Fémara[tiab]	2.498
#8	**Everolimus[Mesh]** OR Everolimus[tiab] OR SDZ RAD[tiab] OR RAD, SDZ[tiab] OR SDZ-RAD[tiab] OR Certican[tiab] OR Zortress[tiab] OR RAD 001[tiab] OR 001, RAD[tiab] OR RAD001[tiab] OR Afinitor[tiab]	8.764
#9	**Immunotherapy, Active[Mesh]** OR Immunotherap*[tiab] OR (immun*[tiab] AND therap*[tiab])	696.271
#10	Tyrosine kinase inhibitor[tiab] OR TKI[tiab]	24.860
#11	**Sorafenib[Mesh]** OR Sorafenib[tiab] OR Nexavar[tiab] OR BAY 43-9006[tiab] OR BAY 43 9006[tiab] OR BAY 439006[tiab] OR Sorafenib N-Oxide[tiab] OR Sorafenib N Oxide[tiab] OR BAY-673472[tiab] OR BAY 673472[tiab] OR BAY 545-9085[tiab] OR BAY 545 9085[tiab] OR BAY 5459085[tiab] OR BAY-545-9085[tiab] OR BAY5459085[tiab]	11.236
#12	**"lenvatinib" [Supplementary Concept]** OR Lenvatinib[tiab] OR E 7080[tiab] OR E-7080[tiab] OR Lenvima[tiab]	1.710
#13	**regorafenib [Supplementary Concept]** OR Regorafenib[tiab] OR Stivarga[tiab] OR BAY 73-4506[tiab] OR BAY73-4506[tiab] OR BAY-73-4506[tiab]	1.724
#14	**cabozantinib [Supplementary Concept]** OR Cabozantinib[tiab] OR Cometriq[tiab] OR XL 184[tiab] OR XL184 cpd[tiab] OR XL-184[tiab] OR BMS 907351[tiab] OR BMS907351[tiab] OR BMS-907351[tiab]	1.421
#15	**Oxaliplatin[Mesh]** OR Oxaliplatin[tiab] OR Oxaliplatine[tiab] OR Eloxatine[tiab] OR Eloxatin[tiab] OR ACT 078[tiab] OR ACT-078[tiab] OR ACT078[tiab]	14.592
#16	**Cisplatin[Mesh]** OR cisplatin[tiab] OR cis-Diamminedichloroplatinum(II)[tiab] OR Platinum Diamminodichloride[tiab] OR Diamminodichloride, Platinum[tiab] OR cis-Platinum[tiab] OR cis Platinum[tiab] OR Dichlorodiammineplatinum[tiab] OR cis-Diamminedichloroplatinum[tiab] OR cis Diamminedichloroplatinum[tiab] OR cis-Dichlorodiammineplatinum(II)[tiab] OR NSC-119875[tiab] OR	16.852

	Platino[tiab] OR Platinol[tiab] OR Biocisplatinum[tiab] OR Platidiam[tiab]	
#17	**Carboplatin[Mesh]** OR Carboplatin[tiab] OR cis-Diammine(cyclobutanedicarboxylato)platinum II[tiab] OR CBDCA[tiab] OR Paraplatin[tiab] OR Paraplatine[tiab] OR Platinwas[tiab] OR Ribocarbo[tiab] OR Carboplat[tiab] OR Neocarbo[tiab] OR Carbosin[tiab] OR Carbotec[tiab] OR Ercar[tiab] OR JM-8[tiab] OR JM 8[tiab] OR JM8[tiab] OR Nealorin[tiab] OR NSC-241240[tiab] OR NSC 241240[tiab] OR NSC241240[tiab] OR Blastocarb[tiab]	20.072
#18	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	785.666
#19	#7 AND #18	2.278
Filter		
#20	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	801.825

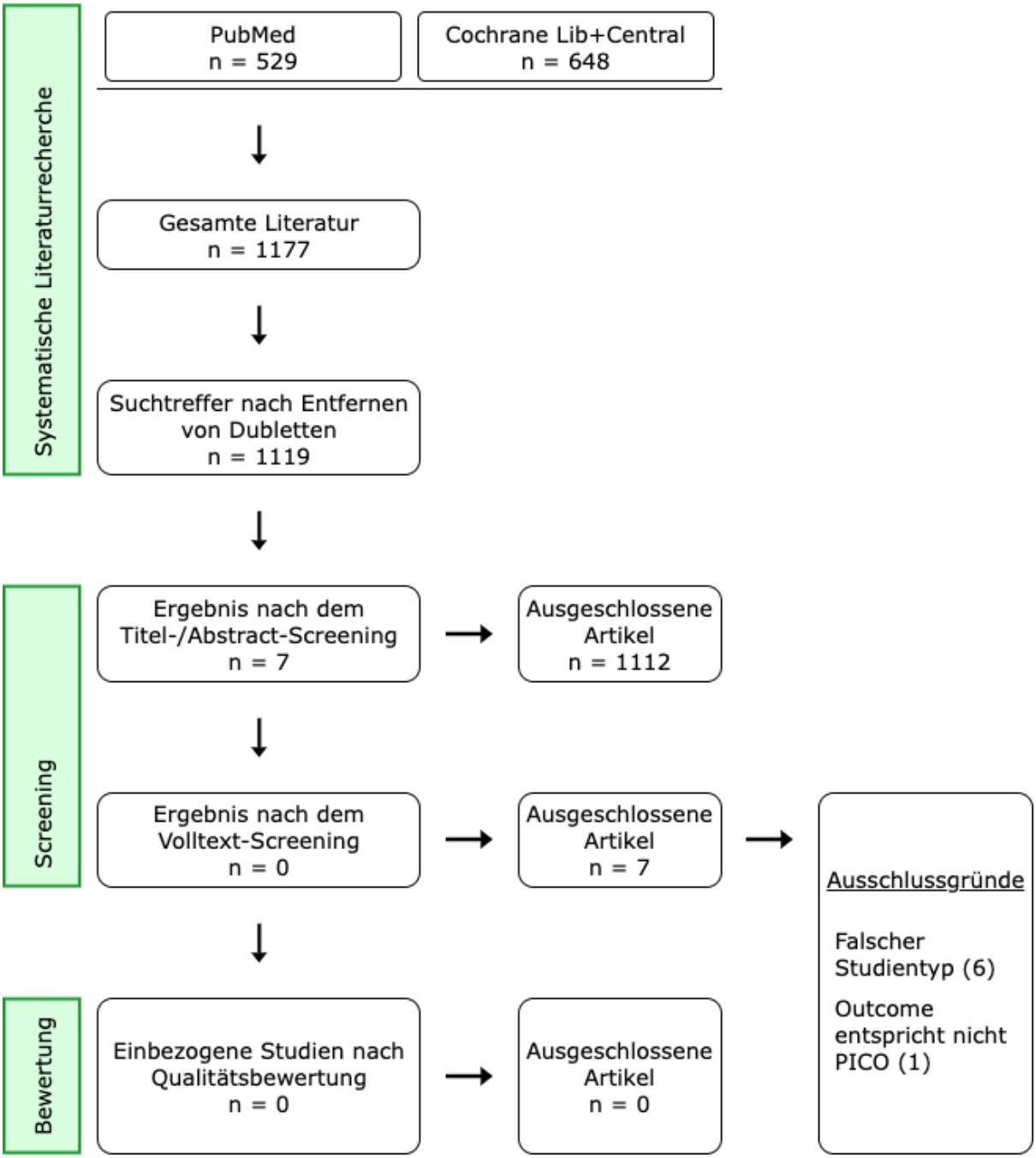
#21	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.674.562
#22	“Case-Control Studies”[Mesh:noexp] OR "retrospective studies"[mesh:noexp] OR “Control Groups”[Mesh:noexp] OR (case[TIAB] AND control[TIAB]) OR (cases[TIAB] AND controls[TIAB]) OR (cases[TIAB] AND controlled[TIAB]) OR (case[TIAB] AND comparison*[TIAB]) OR (cases[TIAB] AND comparison*[TIAB]) OR “control group”[TIAB] OR “control groups”[TIAB] OR cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR Cross-Sectional Studies[Mesh:noexp] OR cross-sectional[TIAB] OR Prevalence[mesh:noexp] OR prevalence[tiab] OR transversal study[tiab]	5.036.868
#23	#20 OR #21 OR #22	6.532.307
#24	animals[mh] NOT humans[mh]	5.055.622
#25	#23 NOT #14	6.230.218
#26	#19 AND #25	791
#27	**Publication date from 01/01/2015 to 31/10/2022, English and German articles, Abstract available**	**529**

Recherche in der Cochrane Library (12.12.2022)

ID	Search	Hits
#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	2055
#2	(Carcinoma, Hepatocellular OR Hepatocellular Carcinoma OR HCC OR Hepatom* OR ((Carcinoma* OR Cancer OR cancers) AND (hepatocellular OR liver cell OR adult liver))):ti,ab,kw	12570

#3	MeSH descriptor: [Cholangiocarcinoma] explode all trees	266
#4	(Cholangiocarcinoma* OR CCA OR Cholangiocellular Carcinoma OR Carcinoma, Cholangiocellular OR Carcinomas, Cholangiocellular OR Cholangiocellular Carcinoma*):ti,ab,kw	1283
#5	#1 OR #2 OR #3 OR #4	13628
#6	(combined OR mixed):ti,ab,kw	180403
#7	#5 AND #6	2974
#8	(combined HCC OR combined CCA OR mixed HCC OR mixed CCA OR cHCC-CCA OR Fibrolamellar hepatocellular carcinoma):ti,ab,kw	831
#9	#7 OR #8	2981
#10	(systemic therap*):ti,ab,kw	35538
#11	MeSH descriptor: [Letrozole] explode all trees	774
#12	(Letrozol* OR CGS 20267 OR CGS-20267 OR CGS20267 OR Femara OR Fémara):ti,ab,kw	2471
#13	MeSH descriptor: [Everolimus] explode all trees	1645
#14	(Everolimus OR SDZ RAD OR RAD, SDZ OR SDZ-RAD OR Certican OR Zortress OR RAD 001 OR 001, RAD OR RAD001 OR Afinitor):ti,ab,kw	4525
#15	MeSH descriptor: [Immunotherapy, Active] explode all trees	3002
#16	(Immunotherap* OR (immun* AND therap*)):ti,ab,kw	88433
#17	(Tyrosine kinase inhibitor OR TKI):ti,ab,kw	3906
#18	MeSH descriptor: [Sorafenib] explode all trees	540
#19	(Sorafenib OR Nexavar OR BAY 43 9006 OR BAY 439006 OR Sorafenib N-Oxide OR Sorafenib N Oxide OR BAY 673472 OR BAY 545 9085 OR BAY 5459085 OR BAY5459085):ti,ab,kw	2058
#20	(Lenvatinib OR E 7080 OR E-7080 OR Lenvima):ti,ab,kw	631
#21	(Regorafenib OR Stivarga):ti,ab,kw	618
#22	(Cabozantinib OR Cometriq OR XL 184 OR XL184 cpd OR XL-184 OR BMS 907351 OR BMS907351 OR BMS-907351):ti,ab,kw	478
#23	MeSH descriptor: [Oxaliplatin] explode all trees	1407
#24	(Oxaliplatin OR Oxaliplatine OR Eloxatine OR Eloxatin OR ACT 078 OR ACT-078 OR ACT078):ti,ab,kw	5379
#25	MeSH descriptor: [Cisplatin] explode all trees	5328
#26	(cisplatin OR cis-Diamminedichloroplatinum(II) OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR cis-	15793

	Platinum OR cis Platinum OR Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR cis-Dichlorodiammineplatinum(II) OR NSC-119875 OR Platino OR Platinol OR Biocisplatinum OR Platidiam):ti,ab,kw	
#27	MeSH descriptor: [Carboplatin] explode all trees	2636
#28	(Carboplatin OR cis-Diammine(cyclobutanedicarboxylato)platinum II OR CBDCA OR Paraplatin OR Paraplatine OR Platinwas OR Ribocarbo OR Carboplat OR Neocarbo OR Carbosin OR Carbotec OR Ercar OR JM-8 OR JM 8 OR JM8 OR Nealorin OR NSC-241240 OR NSC 241240 OR NSC241240 OR Blastocarb):ti,ab,kw	8587
#29	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	150338
#30	#9 AND #29	1388
#31	#30 with Cochrane Library publication date Between Jan 2015 and Oct 2022, in Cochrane Reviews	3
#32	#30 with Publication Year from 2015 to 2022, in Trials	857
#33	#32 NOT (ct.gov OR ICTRP)	645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Outcome entspricht nicht PICO (1)
Bewertung
Einbezogene Studien nach Qualitätsbewertung
n = 0
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2.5. Neue Frage zur Bestrahlung/Updaterecherche

Frage	Population	Intervention	Alternativmaßnahme	Outcome	Priorität
HCC Profitieren Patienten mit einem auf die Leber beschränkten lokal fortgeschrittenen Tumor von einer SBRT?	Patienten mit einem auf die Leber beschränktes HCC, lokal fortgeschritten	SBRT	Andere Intervention (TACE, RFA, TARE) Operation	Progression free survival (lokaler Tumorherd, lokale Ansprechrate)	9
				Overall survival	8
				Adverse Events	7
				Quality of life	7

Einschlusskriterien	
Zielgruppe	Patienten mit hepatozellulärem Karzinom
Publikationstyp	Randomisierte kontrollierte Studien (RCTs) oder systematische Übersicht mit/ohne Metaanalyse oder RCTs, im weiteren Verlauf Fall Kontrollstudien, Kohortenstudien
Sprachen	Deutsch oder Englisch
Suchzeitraum	01.01.2019-31.10.2022

Suche in PubMed (12.12.2022)

Nr	Query	Hits
Population		
#1	**Carcinoma, Hepatocellular[Mesh]** OR HCC[tiab] OR Hepatom*[tiab] OR ((Carcinoma*[tiab] OR Cancer[tiab] OR cancers[tiab]) AND (hepatocellular[tiab] OR liver cell[tiab] OR adult liver[tiab]))	172.763
#2	(**Neoplasms[Mesh]** OR Neoplas*[tiab] OR Tumor[tiab] OR Tumors[tiab] OR Cancer*[tiab] OR Malignanc*[tiab]) AND (hepatocellular[tiab] OR hepatic*[tiab] OR liver*[tiab] OR "**Liver"[Mesh**])	326.695
#3	**Liver Cirrhosis[Mesh]** OR ((liver[Mesh]) AND ("Fibrosis"[Mesh] OR cirr*[tiab] OR fibrosis[tiab]))	113.532
#4	#1 OR #2 OR #3	466.886
Intervention		

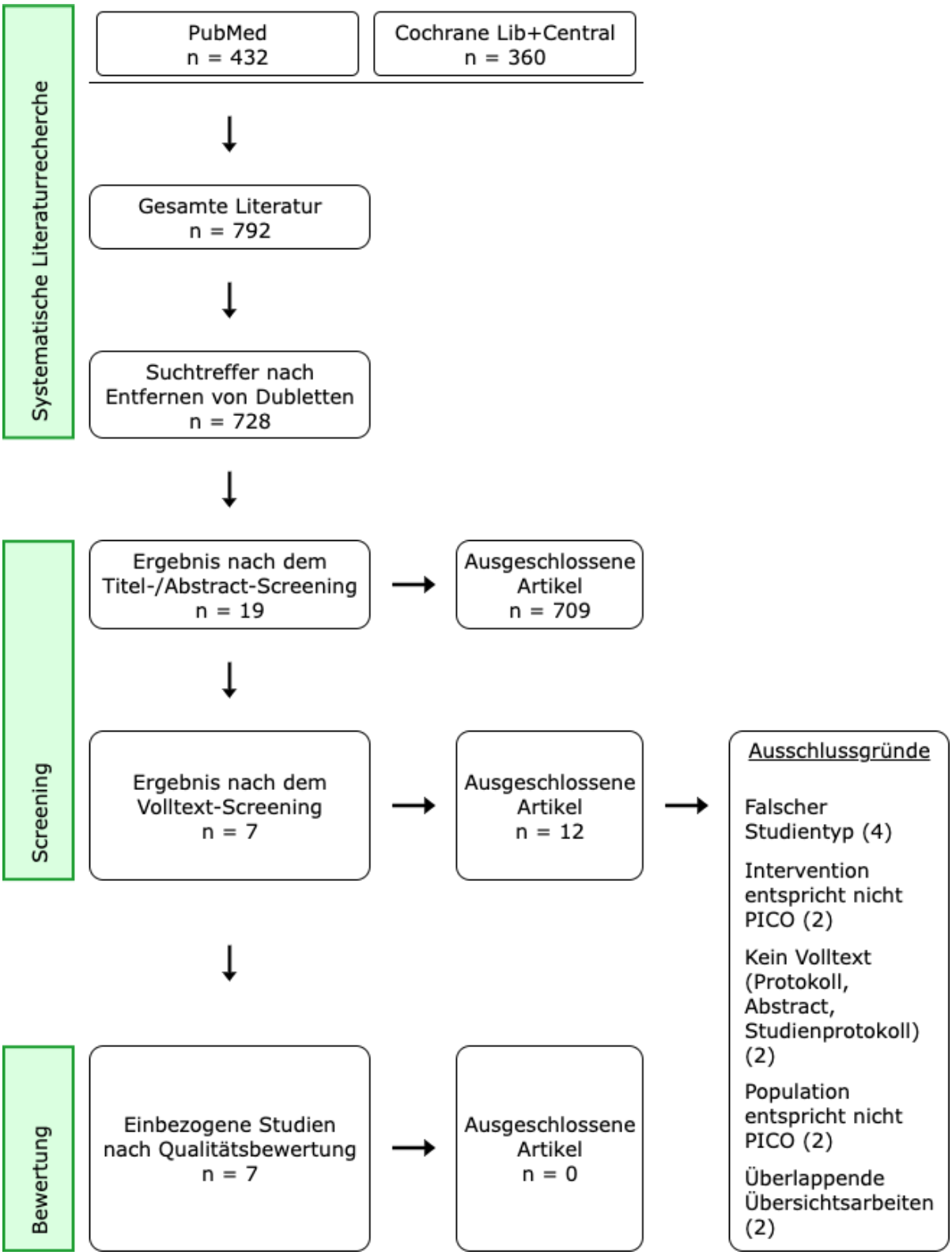
#5	**Radiosurgery[Mesh]** OR Stereotactic body radiation therap*[tiab] OR SBRT[tiab] OR Gamma Knife Radiosurgery[tiab] OR Radiosurgery, Gamma Knife[tiab] OR Gamma Knife Radiosurgeries[tiab] OR Stereotactic Radiation[tiab] OR Radiation, Stereotactic[tiab] OR Stereotactic Radiations[tiab] OR Stereotactic Radiosurgery[tiab] OR Radiosurgery, Stereotactic[tiab] OR Stereotactic Radiosurgeries[tiab] OR Radiosurgery, Linear Accelerator[tiab] OR Linear Accelerator Radiosurgeries[tiab] OR LINAC Radiosurgery[tiab] OR LINAC Radiosurgeries[tiab] OR Radiosurgery, LINAC[tiab] OR Linear Accelerator Radiosurgery[tiab] OR Stereotactic Body Radiotherapy[tiab] OR Radiotherapy, Stereotactic Body[tiab] OR Stereotactic Body Radiotherapies[tiab] OR CyberKnife Radiosurgery[tiab] OR CyberKnife Radiosurgeries[tiab] OR Radiosurgery, CyberKnife[tiab] OR Stereotactic Radiation Therapy[tiab] OR Radiation Therapy, Stereotactic[tiab] OR Stereotactic Radiation Therapies[tiab] OR Therapy, Stereotactic Radiation[tiab] OR Proton beam radiotherap*[tiab] OR three-dimensional conformal radiotherap*[tiab] OR Stereotactic Body Radiotherap*[tiab] OR External Beam Radiation Therap*[tiab] OR radiotherap*[tiab] OR **"Radiotherapy"[Mesh]**	338.433
#6	#4 AND #5	11.719
Filter		
#7	(systematic*[tiab] AND (bibliographic*[tiab] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[tiab] AND (bibliographic*[tiab] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR “meta-analysis as topic”[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])	802.839

#8	"Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[tiab] OR randomized[tiab]) AND (trial[tiab] OR trials[tiab])) OR ((single[tiab] OR double[tiab] OR doubled[tiab] OR triple[tiab] OR tripled[tiab] OR treble[tiab] OR treble[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR ("4 arm"[tiab] OR "four arm"[tiab])	1.675.171
#9	#7 OR #8	2.311.324
#10	animals[mh] NOT humans[mh]	5.070.413
#11	#9 NOT #10	2.269.586
#12	#6 AND #11	1.964
#13	**Publication date from 01/01/2019 to date 31.10.2022, English and German articles, Abstract available**	**432**

Recherche in der Cochrane Library (13.12.2022)

ID	Search	Hits
#1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	2055
#2	(Carcinoma, Hepatocellular OR hepatocellular carcinoma OR HCC OR Hepatom* OR ((Carcinoma* OR Cancer OR cancers) AND (hepatocellular OR liver cell OR adult liver))):ti,ab,kw	12571
#3	MeSH descriptor: [Neoplasms] explode all trees	90536
#4	(Neoplas* OR Tumor OR Tumors OR Cancer* OR Malignanc* OR carcinom):ti,ab,kw	241714
#5	#3 OR #4	252906
#6	MeSH descriptor: [Liver] explode all trees	3504
#7	(hepatocellular OR hepatic* OR liver*):ti,ab,kw	68319
#8	#6 OR #7	68341
#9	#5 AND #8	20215
#10	MeSH descriptor: [Liver Cirrhosis] explode all trees	3228
#11	MeSH descriptor: [Liver] explode all trees	3504

#12	(liver OR hepat*):ti,ab,kw	83992
#13	#11 OR #12	84011
#14	MeSH descriptor: [Fibrosis] explode all trees	6562
#15	(cirrh* OR fibros* OR fibrot*):ti,ab,kw	26648
#16	#14 OR #15	28394
#17	#13 AND #16	13095
#18	#1 OR #2 OR #9 OR #10 OR #17	32756
#19	MeSH descriptor: [Radiosurgery] explode all trees	274
#20	MeSH descriptor: [Radiotherapy] explode all trees	6706
#21	(Radiosurgery OR Stereotactic body radiation therap* OR SBRT OR Gamma Knife Radiosurgery OR Radiosurgery, Gamma Knife OR Gamma Knife Radiosurgeries OR Stereotactic Radiation OR Radiation, Stereotactic OR Stereotactic Radiations OR Stereotactic Radiosurgery OR Radiosurgery, Stereotactic OR Stereotactic Radiosurgeries OR Radiosurgery, Linear Accelerator OR Linear Accelerator Radiosurgeries OR LINAC Radiosurgery OR LINAC Radiosurgeries OR Radiosurgery, LINAC OR Linear Accelerator Radiosurgery OR Stereotactic Body Radiotherapy OR Radiotherapy, Stereotactic Body OR Stereotactic Body Radiotherapies OR CyberKnife Radiosurgery OR CyberKnife Radiosurgeries OR Radiosurgery, CyberKnife OR Stereotactic Radiation Therapy OR Radiation Therapy, Stereotactic OR Stereotactic Radiation Therapies OR Therapy, Stereotactic Radiation OR Proton beam radiotherap* OR three-dimensional conformal radiotherap* OR Stereotactic Body Radiotherap* OR External Beam Radiation Therap* OR radiotherap* OR "Radiotherapy"):ti,ab,kw	38463
#22	#19 OR #20 OR #21	38966
#23	#18 AND #22	2339
#24	#23 with Cochrane Library publication date Between Jan 2019 and Oct 2022, in Cochrane Reviews	2
#25	#23 with Publication Year from 2019 to 2022, in Trials	644
#26	#25 NOT (clinicaltrials.gov OR CT.gov OR ICTRP)	358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Ergebnis nach dem Volltext-Screening
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Ausgeschlossene Artikel
n = 12
Ausschlussgründe
Falscher Studientyp (4)
Intervention entspricht nicht PICO (2)
Kein Volltext (Protokoll, Abstract, Studienprotokoll) (2)
Population entspricht nicht PICO (2)
Überlappende Übersichtsarbeiten (2)
Bewertung
Einbezogene Studien nach Qualitätsbewertung
n = 7
Ausgeschlossene Artikel
n = 0

3. Evidenztabellen

3.1. Update HCC Diagnostik

Inhalt: *8 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Chen, X. 2022	2	Systematic review and META-Analysis of 10 diagnostic studies (with reference standard (blinding n.s.)
Fraquelli, M. 2022	1	Systematic review and META-Analysis of 23 diagnostic studies (with reference standard and blinding)
Kim, Y. Y. 2022	1	Systematic review and META-Analysis of 7 diagnostic studies (with reference standard (blinding n.s.)
Schellhaas, B. 2021	2	Prospective nation-wide multi-center trial (NCT03405909)
Schellhaas, B. 2021	2	Prospective multi-center real-life setting.
Strobel, D. 2021	2	Prospective diagnostic (multicenter real-life setting) study
van der Pol, C. B. 2022	1	Systematic review and IPD META-Analysis of 32 diagnostic studies (with reference standard (blinding n.s.)
Zhou, Y. 2022	1	Systematic review and META-Analysis of 43 diagnostic studies (with reference standard (blinding n.s.))

OXFORD (2011) - AMSTAR 2: Systematic Reviews: *5 Bewertung(en)*

Chen, X. et al. 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). 47. 2057-2070. 2022

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Overall confidence in the results of the review:** AMSTAR II critical appraisal tool for systematic reviews: Two critical flaws (items 7 and 13), two non-critical flaws (items 10 and 12) Overall quality of evidence: critically low **Oxford CEBM Levels of Evidence (2011):** Systematic review of diagnostic studies with reference standard). Downgraded one level due to "Critically low" quality of the AMSTAR appraisal (risk of bias analysis was performed, but the results not discussed or analyzed in regard towards the study results and excluded studies not listed). **Study type:** Systematic review and META-Analysis of 10 diagnostic studies (with reference standard (blinding n.s.) **Databases:** Pubmed/Medline, Embase, the Web of Science, and the Cochrane Library.	**Population:** Adult patients with chronic liver diseases. **Intervention:** head-to-head comparison between ECA-MRI and contrast-enhanced CT. **Comparison:** Reference/Gold standard: Pathological evidence, Biopsy, Excision.	**Primary:** The diagnostic performance of ECA-MRI and contrast-enhanced CT. **Secondary:** - **Results:** In total, 1333 subjects (73.7% male) with 1807 lesions were included. In addition to 4 (40%) retrospective studies, 6 (60%) studies were based on prospective design. ECA-MRI displayed increased sensitivity to contrast-enhanced CT in detecting HCC (0.77 vs. 0.63, P ECA-MRI yielded higher diagnostic accuracy (sAUCs=0.88 vs. 0.80, P In the subgroup analysis with a lesion size	- Di Martino M (2013) European Radiology. - Golferi R (2009) Radiologia Medica. - Hassan A (2011) Egyptian Journal of Radiology and Nuclear Medicine. - Khalili K (2011) Journal of Hepatology. - Basha MAA (2018) European Radiology. - Min JH (2020) Clinical Gastroenterology and Hepatology. - Ronot M (2018) Journal of Hepatology. - Leoni S (2010) American Journal of Gastroenterology.

Search period: up to 1/5/2021. **Inclusion Criteria:** (1) the diagnostic performance of ECA-MRI and contrast-enhanced CT in adult patients with chronic liver diseases for diagnosing HCC was investigated; (2) the diagnose of HCC was established based on the histopathologic evidence and/or imaging follow-up period of at least 6 months; (3) the paired data of the studies with head-to-head comparison of contrast-enhanced CT and ECA-MRI was suficient to construct 2 × 2 table of test performance; and (4) the original articles can be retrieved from SCI journals. **Exclusion Criteria:** (1) the original articles did not assess the accuracy of contrast-enhanced CT and ECA-MRI; (2) conference abstracts, case report, commentary, letter, review or meta-analysis and other special types of work were not considered; (3) no head-to-head comparisons of contrast enhanced CT and ECA-MRI exists.		**Author's Conclusion:** All in all, the current study confirms ECA-MRI showed higher sensitivity but similar specificity with contrast enhanced CT in diagnosing HCC. ECA-MRI outperformed contrast-enhanced CT in per-lesion sensitivity in detecting small HCC (lesions size	- Sangiovanni A (2010) Gut. - Sersté T (2012) Hepatology,	

Fraquelli, M. et al. Contrast-enhanced ultrasound for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease. Cochrane Database Syst Rev. 9. Cd013483. 2022

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 1 **Overall confidence in the results of the review:** AMSTAR II critical appraisal tool for systematic reviews: No critical flaws, one non-critical flaws (items 12) Overall quality of evidence: High **Study type:** Systematic review and META-Analysis of 23 diagnostic studies (with reference standard and blinding) **Databases:** Cochrane Library (2021, Issue 11), MEDLINE Ovid (1946 to 5 November 2021), Embase Ovid (1974 to 5 November 2021), LILACS (Bireme; 1982 to 5 November 2021), Science Citation Index – Expanded (1900 to 5 November 2021), and Conference Proceedings Citation Index – Science (1990 to 5 November 2021). Trial registers, grey litertaure. **Search period:** start see databases- 5 th	**Population:** Adults with chronic liver disease, irrespective of aetiology, severity of disease, and duration of illness, with suspicion of having hepatocellular carcinoma The review focused on diagnostic questions related to people with a first diagnosis of hepatocellular carcinoma. **Intervention:** Contrast-enhanced ultrasound (CEUS) **Comparison:** Reference Standard: - pathology of the explanted liver, and - histology of resected or biopsied focal liver lesion with at least a six-month follow-up.	**Primary:** To assess the diagnostic accuracy of contrast-enhanced ultrasound (CEUS) for the diagnosis of hepatocellular carcinoma of any size and at any stage in adults with chronic liver disease, in a surveillance programme or in a clinical setting. **Secondary:** To assess the diagnostic accuracy of CEUS for the diagnosis of resectable hepatocellular carcinoma in people with chronic liver disease and identify potential sources of heterogeneity in the results. **Results:** 23 studies, 6546 participants. **CEUS for hepatocellular carcinoma of any size and stage:** - sensitivity 77.8% (95% CI 69.4% to 84.4%) and - specificity 93.8% (95% CI 89.1% to 96.6%) (23 studies, 6546 participants; very low-certainty evidence). Reference standard:	- de Sio 2014; - Di Carlo 2012; - Ding 2021; - Forner 2008; - Fracanzani 2001; - Giorgio 2007; - Giorgio 2010; - Huang 2020a; - Hwang 2021; - Kan 2010; - Kang 2020; - Kudo 2019; - Li 2019; - Sangiovanni 2010; - Schellhaas 2017; - Shin 2015; - Sporea	

November 2021 **Inclusion Criteria:** - men and women aged 18 years and older with chronic liver disease - all publication languages - cross-sectional study design - all participants should have undergone one of the acceptable reference standards **Exclusion Criteria:** - People with previous diagnosis and treatment of hepatocellular carcinoma make up a distinct group and were excluded here. - We excluded studies of case-control design that compared people with known hepatocellular carcinoma to matched controls		- typical characteristics on cross-sectional multiphasic contrast CT or MRI with a follow-up period of ≥ 6 months, to allow the confirmation of an initial negative result of CT or MRI; - the pathology of the explanted liver in case of transplantation; - the histology of resected focal liver lesion(s), or the histology of biopsied focal liver lesion(s) with a follow-up period of ≥ 6 months to exclude the presence of focal lesions not detected by the index test. **CEUS for resectable hepatocellular carcinoma:** - sensitivity 77.5% (95% CI 62.9% to 87.6%) and - specificity 92.7% (95% CI 86.8% to 96.1%) (13 studies, 1257 participants; low-certainty evidence). Reference standard: - typical characteristics on cross-sectional multiphasic contrast CT or MRI with a follow-up period of ≥ 6 months, to allow the confirmation of an initial negative result of CT or MRI; - the pathology of the explanted liver in case of transplantation; - the histology of resected focal liver	2019; - Strobel 2021; - Sugimoto 2020; - Tan 2020; - Terzi 2018; - Wang 2006; - Zuo 2021; - Di Carlo 2012 (Abstract only); - Giorgio 2010 (Abstract only).	

		lesion(s), or the histology of biopsied focal liver lesion(s) with a follow-up period of ≥ 6 months to exclude the presence of focal lesions not detected by the index test. The observed heterogeneity in the results remains unexplained. The sensitivity analyses, including only studies with clearly prespecified positivity criteria and only studies in which the reference standard results were interpreted with no knowledge of the results about the index test, showed no differences in the results. **Author's Conclusion:** We found that by using CEUS, as an add-on test following abdominal ultrasound, to diagnose hepatocellular carcinoma of any size and stage, 22% of people with hepatocellular carcinoma would be missed, and 6% of people without hepatocellular carcinoma would unnecessarily undergo further testing or inappropriate treatment. As to resectable hepatocellular carcinoma, we found that 23% of people with resectable hepatocellular carcinoma would incorrectly be unresected, while 8% of people without hepatocellular carcinoma would undergo further inappropriate testing or treatment. The uncertainty		

		resulting from the high risk of bias of the included studies, heterogeneity, and imprecision of the results and concerns on their applicability limit our ability to draw confident conclusions.		

Kim, Y. Y. et al. Diagnostic performance of CT versus MRI Liver Imaging Reporting and Data System category 5 for hepatocellular carcinoma: a systematic review and meta-analysis of comparative studies. Eur Radiol. 32. 6723-6729. 2022

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 1 **Overall confidence in the results of the review: Overall confidence in the results of the review:** AMSTAR II critical appraisal tool for systematic reviews: One critical flaw (items 13), two non-critical flaws (items 10 and 12) Overall quality of evidence: LOW (Risk of bias analysis was performed, but the results not discussed or analyzed in regard towards the study results). **Study type:** Systematic review and META-Analysis of 7	**Population:** Patients at high risk for developing HCC as defined by LI-RADS. **Intervention:** Minimum technical parameters of index tests (CT or MRI) recommended by LI-RADS **Comparison:** Reference test: pathology or composite clinical reference standard	**Primary:** Performance of LR-5 for diagnosing HCC (including true-positive, false-positive, true-negative, and false-negative values with both modalities) **Secondary:** - **Results:** A total of 1145 observations with 725 cases of HCC were included in the final analysis. The pooled per-observation sensitivity of LR-5 for diagnosing HCC was higher using MRI (61%; 95% confidence interval [CI], 43–76%; I^2 = 95%) than CT (48%; 95% CI, 31–65%; I^2 = 97%) (p < 0.001). The pooled per-observation specificities of LR-5 did not show statistically significant difference between CT (96%; 95% CI, 92–98%; I^2 = 0%) and MRI (93%; 95% CI, 88–96%; I^2 = 16%) (p = 0.054). In the subgroup analysis, extracellular contrast	- Min JH (2020) Clin Gastroenterol Hepatol. - Chen N (2016) Magn Reson Med Sci. - Kim BR (2017) Radiology. - Basha MAA (2018) Eur Radiol. - An C (2019) Korean J Radiol. - Nakao S (2019) Jpn J Radiol.	

diagnostic studies (with reference standard (blinding n.s.) **Databases:** MEDLINE and EMBASE **Search period:** Inception to April 21, 2021 **Inclusion Criteria:** - comparative studies that directly compared the diagnostic performance of CT and MRI using the LI-RADS. - English-language publications **Exclusion Criteria:** Reviews, case reports, letters, commentaries, errata, meta-analyses, and studies published only as conference abstracts.		agent–enhanced MRI showed significantly higher pooled per-observation sensitivity than gadoxetic acid–enhanced MRI for diagnosing HCC (73% [95% CI, 55–85%] vs. 55% [95% CI, 39–70%]; p = 0.007), without a significant difference in specificity (93% [95% CI, 80–98%] vs. 94% [95% CI, 87–97%]; p = 0.884). **Author's Conclusion:** In conclusion, the LR-5 of MRI showed significantly higher pooled per-observation sensitivity than CT for diagnosing HCC. The pooled per-observation specificities of LR-5 were comparable between the two modalities.	- Yoon JH (2019) J Magn Reson Imaging.	

van der Pol, C. B. et al. CT/MRI and CEUS LI-RADS Major Features Association with Hepatocellular Carcinoma: Individual Patient Data Meta-Analysis. Radiology. 302. 326-335. 2022

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 1 **Overall confidence in the results of the review:** AMSTAR II critical appraisal tool for systematic reviews:	**Population:** Patients at high risk of HCC (hepatic cirrhosis, chronic hepatitis B viral infection, current or prior HCC).	**Primary:** diagnostic accuracy of CT, MRI, or CEUS for HCC using LI-RADS; The percentage of HCC and overall malignancy for each LI-RADS category on CT, MRI and CEUS including 1–5, TIV	see publication	

No critical flaws, three non-critical flaws (items 5, 10 and 14) Overall quality of evidence: Moderate Regarding 6: "All authors agreeing to participate were sent a formal confidentiality agreement explaining that data would be stored securely and only accessed by authorized coinvestigators with a copy of the data contribution form, data extraction sheet, data dictionary, and a list of frequently asked questions." Thereby, data extraction was not performed by review authors?! **Study type:** Systematic review and IPD META-Analysis of 32 diagnostic studies (with reference standard (blinding n.s.) **Databases:** MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Scopus databases. **Search period:** January 2014 to September 2019 **Inclusion Criteria:** No language or publication type restrictions; All CT, MRI, and CEUS studies reporting the percentage of HCC and overall malignancy for LI-RADS categories 1–5, tumor in vein, and malignancy in patients at high risk of HCC (hepatic cirrhosis, chronic hepatitis B viral	**Intervention:** Multiphasic Contrast-Enhanced CT or MRI version 2014, 2017 or 2018; CEUS version 2016 or 2017. **Comparison:** Reference standard: Pathology or CCRS (composite reference standard)	and M. **Secondary:** - **Results:** CT/MRI: A total of 1170 observations obtained with CT in 812 patients from six studies and 3341 observations obtained with MRI in 2639 patients from 17 studies had sufficient data to be incorporated into the model. CEUS: A total of 853 observations were imaged using CEUS in 833 patients from six studies, and assessments of all major features were available. At multivariable analysis of CT/MRI LI-RADS, all major features were associated with HCC, except threshold growth (OR, 1.6; 95% CI: 0.7, 3.6; P = .07). Nonperipheral washout (OR, 13.2; 95% CI: 9.0, 19.2; P = .01) and nonrim arterial phase hyperenhancement (APHE) (OR, 10.3; 95% CI: 6.7, 15.6; P = .01) had stronger associations with HCC than enhancing capsule (OR, 2.4; 95% CI: 1.7, 3.5; P = .03). On CEUS images, APHE (OR, 7.3; 95% CI: 4.6, 11.5; P = .01), late and mild washout (OR, 4.1; 95% CI: 2.6, 6.6; P = .01), and size of at least 20 mm (OR, 1.6; 95% CI: 1.04, 2.5; P = .04) were associated		

infection, current or prior HCC); all liver observations were required to have been categorized using CT/MRI LI-RADS version 2014, 2017, or 2018 or CEUS LI-RADS version 2016 or 2017; **Exclusion Criteria:** n.s.		with HCC. **Author's Conclusion:** In conclusion, the CT/MRI and contrast-enhanced US (CEUS) Liver Imaging Reporting and Data System (LI-RADS) major features have different independent associations with hepatocellular carcinoma (HCC). Arterial phase hyperenhancement and washout pattern have strong independent associations with HCC using CT/MRI and CEUS LI-RADS. Threshold growth was infrequently reported and was not a significant independent predictor of HCC. The utility of ancillary features, which were not included in our study, would benefit from more comprehensive reporting in future research.		

Zhou, Y. et al. Risk Stratification and Distribution of Hepatocellular Carcinomas in CEUS and CT/MRI LI-RADS: A Meta-Analysis. Front Oncol. 12. 873913. 2022

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 1 **Overall confidence in the results of the review:** AMSTAR II critical appraisal tool for systematic reviews: One critical flaw (item 13), two non-critical	**Population:** Patients with high risk for HCC **Intervention:** Contrast-enhanced CT/MRI examination categorized according to CT/MRI LI-RADS	**Primary:** The proportion of HCC within each LI-RADS category detected using CEUS, and the diagnostic performance of each LI-RADS category for the diagnosis of HCC.	see publication	

flaws (items 10 and 12) Overall quality of evidence: Low (Risk of bias analysis was performed, but the results not discussed or analyzed in regard towards the study results.) Notes: 15. publication bias: there is only limited evidence that publication or reporting bias is a major issue for primary diagnostic test accuracy studies. No appropriate test with adequate statistical power to reliably assess publication bias in the context of diagnostic test accuracy systematic reviews. The authors argue, that this is the reason, why they didn't evaluate for publication bias. **Study type:** Systematic review and META-Analysis of 43 diagnostic studies (with reference standard (blinding n.s.)) **Databases:** PubMed, Embase, and Cochrane Central databases. **Search period:** January 2014 to December 2021 **Inclusion Criteria:** (1) patients with high risk for HCC; (2) the observations undergoing contrast-enhanced CT/MRI examination categorized	V2014, V2017, or V2018, or the observations undergoing CEUS classified according to CEUS LI-RADS V2016 or V2017. **Comparison:** Reference standard: pathology or composite clinical reference standard (CCRS, multiple imaging or imaging follow-up).	**Secondary:** - **Results:** There were 15 studies on CEUS LI-RADS involving 6,573 patients with 7,234 lesions, including 5,387 HCCs, 624 non-HCC malignancies, and 1,223 benign lesions. There were 30 studies on CT/MRI LI-RADS involving 5,274 patients with 6,522 lesions, including 4,554 HCCs, 481 non-HCC malignancies, and 1,487 benign lesions. The proportion of HCCs in CEUS LR-5 was 96%, and that in CECT/MRI LR-5 was 95% ($p > 0.05$). The proportion of non-HCC malignancy in CEUS LR-M was lower than that of CT/MRI LR-M (35% vs. 58%, $p = 0.01$). **Diagnostic performance of CEUS and CT/MRI LR-5 for HCCs.** LR-5: Sensitivity (95% CI), CEUS: 73% (67–78); I^2,%: 87 Sensitivity (95% CI), CT/MRI: 69% (64–74), I^2,%: 92, p= 0.32. Specificity(95% CI), CEUS: 92% (86–95), I^2,%: 75 Specificity(95% CI), CT/MRI: 92% (88–94); I^2,%: 86, p= 0.96. Accuracy(95% CI), CEUS: 78% (71–84); I^2,%: 90		

according to CT/MRI LI-RADS V2014, V2017, or V2018, or the observations undergoing CEUS classified according to CEUS LI-RADS V2016 or V2017; (3) the contrast agent for CEUS being SonoVue; and (4) pathology or composite clinical reference standard (CCRS, multiple imaging or imaging follow-up) used as the reference standard **Exclusion Criteria:** (1) studies applied to patients without high risk for HCCs, (2) studies including duplicated data, (3) studies only including HCCs or HCCs and non-HCC malignancies, and (4) studies without sufficient data for inclusion in the pooled analysis.		Accuracy(95% CI), CT/MRI: 76% (72–79); I^2,%: 93, p= 0.54. DOR (95% CI), CEUS: 28.0 (14.2–55.3); I^2,%: 79 DOR (95% CI), CT/MRI: 23.9 (15.8–36.3); I^2,%: 87.3, p= 0.70. AUC CEUS: 0.74; CT/MRI: 0.75. **Diagnostic performance of CEUS and CT/MRI LR-5 for non-HCC malignancies.** LR-5: Sensitivity (95% CI), CEUS: 83% (73–90); I^2,%: 53 Sensitivity (95% CI), CT/MRI: 65% (56–73), I^2,%: 78, p= 0.01. Specificity(95% CI), CEUS: 92% (86–95), I^2,%: 75 Specificity(95% CI), CT/MRI: 92% (88–94); I^2,%: 86, p= 0.96. Accuracy(95% CI), CEUS: 78% (70–84); I^2,%: 90 Accuracy(95% CI), CT/MRI: 76% (72–79); I^2,%: 93, p= 0.54. DOR (95% CI), CEUS: 36.5 (16.6–80.0); I^2,%: 96 DOR (95% CI), CT/MRI: 46.6 (24.9–88.2); I^2,%: 86 p= 0.64. AUC CEUS: 0.87; CT/MRI: 0.73. **Author's Conclusion:** In conclusion, the proportions of HCCs increase with the upshift of LI-RADS categories from		

		LR-1 to LR-5. CEUS LR-3 has a lower proportion of HCCs than CT/MRI LR-3, while CEUS LR-M has a higher proportion of HCCs. CEUS LR-M has a lower proportion of non-HCC malignancies than CT/MRI LR-M. CEUS LR-5 and CT/ MRI LR-5 show comparable diagnostic performances of HCC, while CEUS LR-M has a higher sensitivity of non-HCC malignancies compared with CT/MRI LR-M. CEUS LR-3 has a lower proportion of HCCs than CT/MRI LRM, while CEUS LR-M has a higher proportion of HCCs. Most of HCCs are in CEUS LR-5, LR-M, and LR-4, while most of HCCs are in CT/MRI LR-5 and LR-4. CEUS LR-M has a lower proportion of non-HCC malignancies but a higher proportion of HCCs compared with CT/MRI LR-M.		

OXFORD (2011) QUADAS-2: Diagnostic Accuracy Studies: *3 Bewertung(en)*

Schellhaas, B. et al. Contrast-Enhanced Ultrasound Algorithms (CEUS-LIRADS/ESCULAP) for the Noninvasive Diagnosis of Hepatocellular Carcinoma - A Prospective Multicenter DEGUM Study. Ultraschall Med. 42. 178-186. 2021				
Evidence level/Study Types	**Population**	**Outcomes/Results**		

Evidence level: 2 **Study type:** Prospective nation-wide multi-center trial (NCT03405909)	**Number of patients / samples:** 321 high risk patients **Inclusion criteria:** - patients with known risk for HCC based on the national guideline and presence of a focal liver lesion; - B-mode ultrasound and CEUS; - Histology available **Exclusion criteria:** - Pretreated lesions, - systemic treatment for HCC - contraindications for CEUS - age **Patient population:** In high-risk HCC patients. **Index test:** Diagnostic accuracy of the recently developed CEUS algorithms (ESCULAP). Direct comparison to the "conventional" interpretation of standardized CEUS at the time of the examination. **Reference test:** Histological findings were collected from biopsy or surgery. **Blinding:** n.s.	**Key outcomes:** diagnostic accuracy of standardized contract-enhanced ultrasound (CEUS) for the noninvasive diagnosis of hepatocellular carcinoma (HCC); All lesions had to be categorized according to the two CEUS algorithms ESCULAP (Erlanger Synopsis for ContrastEnhanced Ultrasound for Liver Lesion Assessment in Patients at risk) and CEUS LI-RADS (Contrast-Enhanced UltraSound Liver Imaging Reporting and Data System). **Results:** 299 (93.1 %) had liver cirrhosis. The diagnosis according to histology was HCC in 256 cases, and intrahepatic cholangiocarcinoma (iCCA) in 23 cases. In the subgroup of cirrhotic patients (n = 299), the highest sensitivity for the diagnosis of HCC was achieved with the CEUS algorithm ESCULAP (94.2 %) and CEUS on-site (90.9 %). The lowest sensitivity was reached with the CEUS LI-RADS algorithm (64 %; $p < 0.001$). However, the specificity of CEUS LI-RADS (78.9 %) was superior to that of ESCULAP (50.9 %) and CEUS on-site (64.9 %; $p < 0.001$). At the same time, the negative predictive value (NPV) of CEUS LI-RADS was significantly inferior to that of ESCULAP (34.1 % vs. 67.4 %; $p < 0.001$) and CEUS on-site (62.7 %; $p < 0.001$). The positive predictive values of all modalities were high (around 90 %), with the best results seen for CEUS LI-RADS and CEUS on-site.		

Methodical Notes		
Notes: Result of QUADAS-2 Checklist: Overall: low (unclear/low/unclear/low/low/low/low)		

Schellhaas, B. et al. Contrast-Enhanced Ultrasound Patterns for the Non-invasive Diagnosis of Hepatocellular Carcinoma: A Prospective Multicenter Study in Histologically Proven Liver Lesions in a Real-Life Setting Demonstrating the Benefit of Extended Late Phase Observation. Ultrasound Med Biol. 47. 3170-3180. 2021

Evidence level/Study Types	Population	Outcomes/Results
Evidence level: 2 **Study type:** Prospective multi-center real-life setting.	**Number of patients / samples:** 395 patients with available histology **Inclusion criteria:** Patients at high risk for HCC according to national HCC guidelines with a solid liver lesion visible on B-mode ultrasound - histology available - CEUS diagnosis **Exclusion criteria:** - systemic treatment for HCC - contraindications for CEUS - no informed consent - age < 18 years **Patient population:** Patients at high risk for HCC according to national HCC guidelines with a solid liver lesion visible on B-mode ultrasound.	**Key outcomes:** Validate the findings of the typical HCC pattern (APHE followed by late-onset, mild washout); Sensitivities, specificities and positive and negative predictive values were calculated. **Results:** In total, 395 patients (male/female = 329/66, mean age: 67 y, range: 2988 y) at high risk of HCC with histology-proven lesions were analyzed. Tumor diagnoses based on histology were - hepatocellular carcinoma (HCC), n= 316 (median size: 40 mm); - intrahepatic cholangiocellular carcinoma (iCCA), n = 26 (median size: 47.5 mm); and - other malignancy, n = 19. Overall, 85.8% of HCCs exhibited APHE. APHE followed by washout occurred in 72.8% of HCCs and 50% of iCCAs and non-HCC, non-iCCA malignancies (p 46

	Index test: CEUS (categorization of the index lesion according to the standardized CEUS algorithms ESCULAP and CEUS LI-RADS) **Reference test:** Histology **Blinding:** Patients provide their written consent for prospective evaluation of anonymized data.	min in 10% of cases). The positive predictive value were almost equal for the hyperhypo and the hyperiso patterns for the noninvasive diagnosis of HCC (86.8% vs. 85.4%).		
Methodical Notes				
Notes: Subanalysis of DEGUM study from Shellhaas et al study. Result of QUADAS-2 Checklist: Overall: low (unclear/low/unclear/low/low/low/low)				

Strobel, D. et al. Real-life assessment of standardized contrast-enhanced ultrasound (CEUS) and CEUS algorithms (CEUS LI-RADS®/ESCULAP) in hepatic nodules in cirrhotic patients-a prospective multicenter study. Eur Radiol. 31. 7614-7625. 2021

Evidence level/Study Types	Population	Outcomes/Results		
Evidence level: 2 **Study type:** Prospective diagnostic (multicenter real-life setting) study	**Number of patients / samples:** 395 patients. **Inclusion criteria:** - age ≥ 18 years, the presence of a FLL visible on conventional B-mode ultrasound, - the availability of a reference standard. **Exclusion criteria:** - age < 18 years, - systemic or local treatment for HCC, and - contraindications for CEUS (such as known allergy or	**Key outcomes:** Diagnostic accuracy based on subjective interpretation by an experienced examiner, the definition according to current guidelines ("arterial phase hyperenhancement followed by hypoenhancement"), and the recently developed CEUS algorithms ESCULAP and CEUS LI-RADS. **Results:** The final diagnosis was 378 HCCs and 92 non-HCC lesions (benign, n = 49; malignant, n = 43)		

	hemodynamic instability). **Patient population:** Cirrhotic patients **Index test:** Standardized CEUS algorithms; conventional liver ultrasound, followed by immediate CEUS. **Reference test:** Histology was regarded as the gold standard; in cases with no available histological findings, MRI or CT was used as reference. In cases with both MRI and CT available (n = 23), MRI was used as the reference. There were no inconsistencies in the diagnosis between MRI and CT in these patients. **Blinding:** n.s.	based on the reference (n =470). Histological findings were available in 364 patients (77.4%). MRI and CT served as reference standard in 77 (16.4%) and 29 (6.2%) cases, respectively. Modality **CEUS on-site (subjective)** N (HCC): 378; N (Non-HCC): 92; Sensitivity: 91.5% [88.7%; 94.3%]; Specificity: 67.4% [57.8%; 77%]; PPV*: 92% [89.3%; 94.8%]; NPV*: 66% [56.4%; 75.5%]. **CEUS guidelines (hyper-hypo)** N (HCC): 378; N (Non-HCC): 92; Sensitivity: 74.3% [69.9%; 78.7%]; Specificity: 63% [53.2%; 72.9%]; PPV*: 89.2% [85.8%; 92.6%]; NPV*: 37.4% [29.8%; 45%]. **ESCULAP N (HCC)**: 279; N (Non-HCC): 70; Sensitivity: 95% [92.4%; 97.5%]; Specificity: 51.4% [39.7%; 63.1%]; PPV*: 88.6% [85%; 92.2%]; NPV*: 72% [59.6%; 84.4%]. **CEUS LI-RADS© N (HCC)**: 279; N (Non-HCC): 70; Sensitivity: 65.2% [59.6%; 70.8%]; Specificity 78.6% [69%; 88.2%]; PPV*: 92.4% [88.7%; 96.1%]; NPV*: 36.2% [28.5%; 43.8%]. *Relating to a prevalence of 80%		
Methodical Notes				
Notes: Trial NCT03405909, see also two studies from Schellhaas B et al 2022.				

Result of QUADAS-2 Checklist: Overall: low (unclear/low/unclear/low/low/low/high)		

3.2. HCC Systemtherapie

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. 2022		
Kudo, M. 2022	3	Non-randomised, multicentre, open-label phase II study (KEYNOTE-224 (NCT02702414))
Kudo, M. 2021	3	Phase I/II, open-label clinical trial (Child-Pugh B cohort of CheckMate 040).
Yau, T. 2022	2	CheckMate 459 trial was a multicentre, nivolumab monotherapyrandomised, open-label, phase 3 trial

Cochrane Risk of Bias Tool 1 (RCT): *4 Bewertung(en)*

Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. . Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM. . . 2022			
Population	**Intervention / Comparison**	**Outcomes/Results**	**Methodical Notes**
Evidence level: **Study type:** **Number of Patients:** **Recruiting Phase:** **Inclusion Criteria:** **Exclusion Criteria:**	**Intervention:** **Comparison:**	**Primary:** **Secondary:** **Results:** **Author's Conclusion:**	**Funding Sources:** **COI:** **Randomization:** **Blinding:** **Dropout Rate/ITT-Analysis:** **Notes:** Diese Studie wurde von der DKG entsprechend der GRADE Methodik bewertet.

Kudo, M. et al. Updated efficacy and safety of KEYNOTE-224: a phase II study of pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib. Eur J Cancer. 167. 1-12. 2022			
Population	**Intervention / Comparison**	**Outcomes/Results**	**Methodical Notes**
Evidence level: 3 **Study type:** Non-randomised, multicentre, open-label phase II study (KEYNOTE-224 (NCT02702414)) **Number of**	**Intervention:** Pembrolizumab 200 mg intravenous infusion once every 3 weeks for 35 cycles or until confirmed progression/unacceptable toxicity, patient withdrawal of consent or investigator decision. **Comparison:** -	**Primary:** Objective response rate (ORR) assessed by BICR per RECIST v1.1. **Secondary:** - Duration of response (DOR), - disease control rate (DCR), - time to progression (TTP) and - PFS	**Funding Sources:** The study sponsor, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, funded the study. Additionally, the study sponsor designed the study protocol in collaboration with the Steering Advisory Committee.

Patients: In KEYNOTE-224, 104 patients received 1 dose of pembrolizumab at the final analysis. **Recruiting Phase:** Data cutoff 31. July 2020. **Inclusion Criteria:** - Adults had a histologically or cytologically confirmed diagnosis of HCC, - experienced documented progression after stopping treatment with sorafenib or experienced intolerance to sorafenib, and had - Barcelona Clinic Liver Cancer stage C or B not amenable to or refractory to locoregional therapy and were not amenable to a curative treatment. **Exclusion Criteria:** see evidence		**Results:** Among the treated patients, 10 patients completed treatment. The remaining 94 patients discontinued therapy. The primary reasons for discontinuation were PD in 61 patients and AEs in 24 patients. Four patients received a second course of pembrolizumab. Objective response rate was 18.3% (95% CI: 11.4-27.1), and median duration of response was 21.0 months (range, 3.1 to 39.5). Disease control rate was 61.5%, and median time to progression was 4.8 months (95% CI: 3.9-7.0). Median progression-free survival was 4.9 months (95% CI: 3.5-6.7) and median overall survival was 13.2 months (95% CI: 9.7-15.3). Of 104 patients, 76 (73.1%) patients reported treatment-related adverse events; most were low grade in severity (grade 3-4, n=26 [25.0%]; grade 5, n=1 [1.0%]). Immune-mediated hepatitis occurred in 3 patients (all grade 3). No viral-induced hepatitis flares occurred.	**COI:** see full text **Randomization:** none **Blinding:** none **Dropout Rate/ITT-Analysis:** **Notes:** The presented analysis is a follow-up analysis of Zhou et al 2018 (appraised in Key question HCC 20 Systemtherapie on www.guideline-service.de) and reports efficacy and safety data for KEYNOTE-224 with w2.5 years of additional follow-up, including outcomes for patients receiving a second course of pembrolizumab following disease progression after the first course of pembrolizumab. ROB assessment: - no enough details presented here, but initial study was evaluated with low risk of bias. Since this is a follow-up analysis we take over the analysis of the original study of Zhou et al 2018. Overall assessment - low risk of bias. **Oxford CEBM Levels of Evidence (2011):** Non-randomized controlled cohort.

table of original publication.		**Author's Conclusion:** Extended follow-up from KEYNOTE-224 demonstrated that pembrolizumab provides robust and durable efficacy in patients with advanced HCC who were previously treated with sorafenib. Taken together with the consistent safety profile for pembrolizumab, this report confirms the favourable benefit-risk of pembrolizumab in this population.	

Kudo, M. et al. CheckMate 040 cohort 5: A phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis. J Hepatol. 75. 600-609. 2021

Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Phase I/II, open-label clinical trial (Child-Pugh B cohort of CheckMate 040). **Number of Patients:** 49 patients with aHCC in the Child-Pugh B cohort of CheckMate 040 were enrolled and included in the analysis (patients from 27 sites in 5 countries). **Recruiting Phase:** August 19, 2016, and October 27,	**Intervention:** Nivolumab 240 mg flat dose intravenously for 30 min every 2 weeks until unacceptable toxicity or disease progression per RECIST v1.1. On-treatment safety procedures included physical examinations, Child-Pugh B score assessment, and evaluation of adverse events (AEs), concurrent medications, and vital signs. Efficacy procedures included tumour imaging (computed tomography or magnetic resonance	**Primary:** ORR based on investigator assessment using RECIST v1.1 and duration of response (DOR). **Secondary:** Disease control rate (DCR), time to response (TTR), time to progression (TTP), TTP rate, progression-free survival (PFS), OS, OS rate, and association between biomarkers and efficacy. Patient-reported outcomes (PROs), the 3-level version of the EQ-5D (EQ-5D-3L) and FACT-Hep questionnaires were administered before clinical activities at baseline on cycle 1 day 1 and every other	**Funding Sources:** This study was supported by Bristol Myers Squibb (Princeton, NJ) and by Ono Pharmaceutical Co., Ltd. (Osaka, Japan). **COI:** See publication. **Randomization:** no. **Blinding:** no. **Dropout Rate/ITT-Analysis:** 2 patients (4%) **Notes:** ROB assessment according to ROBINS-I Tool: - Confounding, might be at high risk because no

2017. **Inclusion Criteria:** - Child-Pugh B (B7–B8) histologically confirmed aHCC not eligible for surgical and/or locoregional therapy. - no prior sorafenib treatment or documented radiographic progression on or intolerance of sorafenib; - Eastern Cooperative Oncology Group performance status of 0 or 1; - no to mild ascites; - >=1 untreated lesion measurable by Response Evaluation Criteria in Solid Tumors - non-viral HCC or HBV or HCV infection **Exclusion Criteria:** - known fibrolamellar HCC, - sarcomatoid HCC, or mixed cholangiocarcinoma and HCC; history of hepatic encephalopathy within 2 weeks of screening; - history of hepatorenal syndrome; paracentesis for treatment of ascites within 2 weeks of screening;	imaging) every 6 weeks for up to 48 weeks, and every 12 weeks thereafter. **Comparison:** -	cycle thereafter. **Results:** Most patients had a Child-Pugh score of B7 (76%), and the model for end-stage liver disease-sodium (MELD-Na) median score was 12 (interquartile range, 10–14). All 49 patients were treated with nivolumab (n= 25 were sorafenib naive, n= 24 were sorafenib treated). Disease progression was the most common reason for treatment discontinuation (78%). No treatment-related deaths were reported. Investigator assessed ORR was 12% (95% CI 5–25%) with 6 patients responding; disease control rate was 55% (95% CI 40–69%). Median time to response was 2.7 months (interquartile range, 1.4–4.2), and median duration of response was 9.9 months (95% CI 9.7–9.9). Treatment-related adverse events (TRAEs) were reported in 25 patients (51%) and led to discontinuation in 2 patients (4%). The most frequent grade 3/4 TRAEs were hypertransaminasemia (n = 2), amylase increase (n = 2), and aspartate aminotransferase increase (n = 2). The safety of nivolumab was comparable to that in patients with Child-Pugh A aHCC.	confounding applied. However, due to the phaseI/II status and ethical considerations we didn't take this into account here. - Other Bias domains are at low risk of bias. Overall assessment - low risk of bias. **Oxford CEBM Levels of Evidence (2011):** Non-randomized controlled cohort.

- active brain or leptomeningeal metastases; active co-infection with both HBV and HCV; - prior liver transplant.		**Author's Conclusion:** Nivolumab showed clinical activity and manageable safety in patients with Child-Pugh B class aHCC compared with historical data, suggesting that the use of nivolumab monotherapy in this patient population warrants further investigation. Stable liver function was observed in patients with clinical benefit based on Child-Pugh scores and ALBI grade over time. Among responders, Child-Pugh scores improved over time, and all responders maintained stable ALBI grades for >−6 months.	

Yau, T. et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. The lancet. Oncology. 23. 77?90. 2022

Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 2 **Study type:** CheckMate 459 trial was a multicentre, nivolumab monotherapyrandomised, open-label, phase 3 trial **Number of Patients:** 1320 patients were screened via medical centres in 22 countries and territories in Asia, Australasia, Europe, and North America; 743 patients were randomly assigned (n= 371	**Intervention:** Nivolumab monotherapy (240 mg intravenously every 2 weeks) or **Comparison:** Sorafenib monotherapy (400 mg orally twice daily) until disease progression (by RECIST version 1.1),11 unacceptable toxicity, withdrawal of consent, or study closure.	**Primary:** Overall survival (time from randomisation date to last known date alive or death). **Secondary:** - Objective response - Progression-free survival - Efficacy (overall survival, progression-free survival, and objective response) based on baseline tumour cell PD-L1 expression.	**Funding Sources:** The funder of the study had a role in study design; data collection, data analysis, and data interpretation; and writing of the report. Bristol Myers Squibb in collaboration with Ono Pharmaceutical. **COI:** see publication **Randomization:** Patients were randomly assigned (1:1) to receive nivolumab or sorafenib. The sponsor's Interactive Response Technology Group created the

nivolumab, n= 372 sorafenib). **Recruiting Phase:** Jan 11, 2016, to May 24, 2017 **Inclusion Criteria:** - Patients with advanced hepatocellular carcinoma in the first-line setting; - at least 18 years old with histologically confirmed advanced hepatocellular carcinoma not eligible for, or whose disease had progressed after, surgical or locoregional therapies; - Child-Pugh class A, - Eastern Cooperative Oncology Group performance status score of 0–1, - no previous systemic therapy for hepatocellular carcinoma, - no previous radiotherapy within 4 weeks before study drug commencement - availability of fresh or archival tumour tissue for analysis. **Exclusion Criteria:** Patients were ineligible if they had fibrolamellar or sarcomatoid hepatocellular carcinoma, mixed cholangiocarcinoma and hepatocellular carcinoma, previous liver transplant, history of hepatic encephalopathy,		**Results:** Median follow-up for overall survival was 15.2 months (IQR 5.7–28.0) in the nivolumab group and 13.4 (5.7–25.9) in the sorafenib group. Disease progression was the most common reason for nivolumab or sorafenib discontinuation. **Overall survival:** Nivolumab 244/372, Sorafenib 275/372; Median overall survival was 16.4 months (95% CI 13.9–18.4) with nivolumab and 14.7 months (11.9–17.2) with sorafenib: HR 0.85 (0.72-1.02), p=o.075. 12-months OS: Nivolumab: 60% (54-65%), Sorafenib: 55% (50-60%). 18-months OS: Nivolumab: 47% (41-52%), Sorafenib: 44% (38-49%). 24 months OS: Nivolumab: 37% (32-42%), Sorafenib: 33% (28-38%). **Objective response:**	computer-generated patient randomisation schedule on the basis of the protocol requirements as approved by the sponsor's Biostatistics and Data Sciences Group. Randomisation was done at a central location across all participating countries, with patients stratified according to cause, vascular invasion or extrahepatic spread, and geography (Asia vs non-Asia). Randomisation procedures were done via permuted blocks with a block size of four within each stratum. **Blinding:** Patients and investigators were not masked to treatment allocation. **Dropout Rate/ITT-Analysis:** Sorafenib: n= 372 analyzed for efficacy, n= 363 analyzed for safety; Nivolumab n= 371 analyzed for efficacy, n= 367 analyzed for safety. **Notes:** Cochrane risk of bias tool (Rob)-1: 0 questions(s) were considered to be unclear risk of bias; 0 question(s) were considered to be high risk of bias. Overall risk of bias: Low. **Oxford CEBM Levels of Evidence (2011):** Randomized controlled trial.

clinically significant ascites, portal hypertension with bleeding, oesophageal or gastric varices within the past 6 months, or active brain metastases.		Nivolumab: 57/371 (15%, 12-19%), Sorafenib: 26/372 (7%, 5-10%). **Progression free survival:** Nivolumab 305/372, Sorafenib 288/372; HR 0.93 (0.79-1.10). 12-months PFS: Nivolumab: 22% (18-27%), Sorafenib: 14% (10-18%). 18-months PFS: Nivolumab: 17% (13-21%), Sorafenib: 9% (6-13%). 24 months PFS: Nivolumab: 14% (10-18%), Sorafenib: 6% (3-10%). The absolute numbers of patients who died were 242 (66%) in the nivolumab group and 270 (74%) in the sorafenib group, with disease progression as the primary cause of death in both groups (204 [56%] with nivolumab and 235 [65%] with sorafenib). **Adverse events:** The most common grade 3 or worse treatment-related adverse events were palmar-plantar erythrodysaesthesia (1 [	

		Four deaths in the nivolumab group and one death in the sorafenib group were assessed as treatment related. **Author's Conclusion:** In conclusion, nivolumab monotherapy did not significantly prolong overall survival compared with sorafenib as first-line treatment for patients with advanced hepatocellular carcinoma. However, nivolumab showed durable clinical activity in terms of response frequency and durability, with encouraging long-term survival, a differentiated and favourable safety profile with no new safety signals, and clinically meaningful improvements in HRQOL. Nivolumab is being further investigated in different treatment settings in hepatocellular carcinoma and in combination with other drugs and procedures to evaluate its efficacy and safety.	

3.3. CCA Systemtherapie

Inhalt: *4 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Choi, I. S. 2021	2	Randomised, open-label, multicentre, phase 2 trial.
Do-Youn Oh, M.D., Ph.D.1, Aiwu Ruth He, M.D., Ph.D.2, Shukui Qin, M.D.3, Li-Tzong Chen, M.D., Ph.D.4,5,6, Takuji Okusaka, M.D., Ph.D.7, Arndt Vogel, M.D.8, Jin Won Kim, M.D., Ph.D.9, Thatthan Suksombooncharoen, M.D.10, Myung Ah Lee, M.D., Ph.D.11, Masayuki Kitano, M.D., Ph.D.12, ... ,for the TOPAZ-1 Investigators* 2022		
Luvira, V. 2021	1	Systematic review and META-Analysis of 5 randomized controlled trials.
Oh, D. Y. 2022		

OXFORD (2011) - AMSTAR 2: Systematic Reviews: *1 Bewertung(en)*

Luvira, V. et al. Postoperative adjuvant chemotherapy for resectable cholangiocarcinoma. Cochrane Database Syst Rev. 9. Cd012814. 2021				
Evidence level/Study Types	**P - I - C**	**Outcomes/Results**	**Literature References**	
Evidence level: 1 **Overall confidence in the results of the review:** AMSTAR II critical appraisal tool for systematic reviews: No critical flaw, zero non-critical flaws. Overall quality of evidence: high **Oxford CEBM Levels of Evidence (2011):** Systematic review of randomized controlled trials. **Study type:** Systematic review and META-Analysis of 5 randomized controlled trials. **Databases:** Cochrane Hepato- Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE, Embase, LILACS, Science Citation Index Expanded, and Conference Proceedings Citation Index - Science	**Population:** Adults (aged 18 years or older) of any sex who underwent curative intent resection for cholangiocarcinoma and received any type of postoperative adjuvant chemotherapy compared with people with the same condition, but receiving placebo, no postoperative adjuvant chemotherapy, or other adjuvant chemotherapies. **Intervention:** All regimens of postoperative adjuvant chemotherapy (intravenous infusion, intravenous bolus, intraportal infusion, and oral administration of a single regimen or a combination of chemotherapy regimens). **Comparison:** No postoperative adjuvant chemotherapy (surgery alone), placebo, or a different regimen or form of chemotherapy.	**Primary:** - All-cause mortality. - Serious adverse events. - Health-related quality of life. **Secondary:** - Cancer-related mortality (death from cancer). • Time to recurrence of the tumour. • Non-serious adverse events. **Results:** The trials included 931 adults (18 to 83 years old) who underwent curative intent resection for cholangiocarcinoma. Four trials compared postoperative **adjuvant chemotherapy** (mitomycin-C and 5-fluorouracil (5-FU); gemcitabine; gemcitabine plus oxaliplatin; or capecitabine) versus no postoperative adjuvant chemotherapy (surgery alone) in 867 participants with cholangiocarcinoma only. **All cause mortality:** post-op adjuvant chemotherapy versus no	Takada 2002; Ebata 2018; Edeline 2019; Kobayashi 2019; Primrose 2019).	

Search period: up to 28 April 2021 **Inclusion Criteria:** Randomized clinical trials irrespective of blinding, publication status, or language comparing postoperative adjuvant chemotherapy versus placebo, no intervention, or a different postoperative adjuvant chemotherapy regimen for participants with curative-intent resection for cholangiocarcinoma. **Exclusion Criteria:**		post-op adjuvant chemotherapy: RR 0.92, 95% CI 0.84 to 1.01; 4 trials, 867 participants, very low-certainty evidence. **Adverse events:** Serious adverse events: RR 17.82, 95% CI 2.43 to 130.82; 1 trial, 219 participants, very low-certainty evidence. A fifth trial compared **postoperative adjuvant S-1** (a novel oral fluoropyrimidine derivative) chemotherapy versus gemcitabine in 70 participants with intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma (64 participants), and gallbladder carcinoma (6 participants). The authors reported that one-year overall mortality after adjuvant S-1 therapy was lower than with adjuvant gemcitabine-based therapy following major hepatectomy for biliary tract cancer (RR 0.38 (0.15-0.96), 1 trial, 70 patients, very-low certainty of evidence). There were no differences in two-year overall mortality (RR 0.81 (0.58-1.13), 1 trial, 70 patients, very-low certainty of evidence). We assessed all of the included trials at overall high risk of bias. **Author's Conclusion:** Based on the very		

		low-certainty evidence found in four trials in people with curative-intent resection for cholangiocarcinoma, we are very uncertain of the effects of postoperative adjuvant chemotherapy (mitomycin-C and 5-FU; gemcitabine; gemcitabine plus oxaliplatin; or capecitabine) versus no postoperative adjuvant chemotherapy on mortality. The effects of postoperative adjuvant chemotherapy compared with no postoperative adjuvant chemotherapy on serious adverse events are also very uncertain, but the result of the single trial showed 20% higher occurrences of haematologic adverse events. We assessed the certainty of the evidence as very low due to overall high risk of bias, and imprecision. Due to insufficient power of the only identified trial, the best postoperative adjuvant chemotherapy regimen in people with only cholangiocarcinoma could not be established. We also lack randomized clinical trials with outcome data on adjuvant S-1 chemotherapy versus adjuvant gemcitabine-based chemotherapy in people with cholangiocarcinoma alone. There is a need for further randomized clinical trials designed to be at low risk of bias and with adequate sample size exploring the best adjuvant chemotherapy treatment aGer		

		surgery in people with cholangiocarcinoma.		

Cochrane Risk of Bias Tool 1 (RCT): *3 Bewertung(en)*

Choi, I. S. et al. A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. Eur J Cancer. 154. 288-295. 2021

Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 2 **Study type:** Randomised, open-label, multicentre, phase 2 trial. **Number of Patients:** 118 patients with locally advanced or metastatic BTC refractory to first-line gemcitabine/cisplatin chemotherapy were randomized and 59 assigned to each group. **Recruiting Phase:** 24 August 2015 to 5 November 2019. **Inclusion Criteria:** Patients with locally advanced or metastatic BTC refractory to first-line gemcitabine/cisplatin chemotherapy; - histologically confirmed BTC, including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma,	**Intervention:** irinotecan/5-fluorouracil (5-FU; mFOLFIRI, 150 mg/m2 irinotecan for 2 h, 100 mg/m2 leucovorin for 2 h followed by 2400 mg/m2 5-FU for 46 h, every 2 weeks). **Comparison:** Oxaliplatin/5-FU (mFOLFOX, 100 mg/m2 oxaliplatin for 2 h, 100 mg/m2 leucovorin for 2 h followed by 2400 mg/m2 5-FU for 46 h, every 2 weeks).	**Primary:** OS rate at 6 months. **Secondary:** - objective response rate (ORR) - disease control rate (DCR) - PFS - Adverse events **Results: Overall survival:** At a median follow-up duration of 25.8 months [95% CI, 6.1-45.5], the **6-month OS rate as the primary endpoint** was - 54.1% in the mFOLFOX arm and - 44.1% in the mFOLFIRI arm. The median OS was - 6.3 months (95% CI, 4.4-8.2) in the mFOLFOX arm and - 5.7 months (95% CI, 4.7-6.7) in the mFOLFIRI arm (p = 0.677 (logrank test); HR = 1.1 (95% CI, 0.7-1.6), p = 0.683 (Cox regression test)). **Progression free survival:**	**Funding Sources:** This work was supported by HK inno.N Corporation, Korea. Irinotecan and palonosetron were provided by HK inno.N Corporation, Korea. Oxaliplatin was provided by Jeil Pharma, Korea. The funders had no role in study design, data collection and analysis, decision to publish or manuscript preparation. **COI:** No potential conflict of interest was disclosed. **Randomization:** - randomly assigned in a 1:1 ratio to receive either mFOLFOX (control arm) or mFOLFIRI (experimental arm). - Randomisation was stratified by tumour location (intrahepatic versus extrahepatic versus gallbladder versus ampulla of Vater) and ECOG PS (0, 1 versus 2). **Blinding:** n.s. **Dropout Rate/ITT-**

gallbladder cancer and ampulla of Vater cancer; - Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2; - failure to first-line gemcitabine/cisplatin; - measurable or evaluable tumour lesion by the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) and adequate organ function **Exclusion Criteria:** - two or more prior lines of systemic chemotherapy, - other solid tumour history, - pregnancy or lactating woman, - uncontrolled medical disease, - known hypersensitivity history for investigational agents and - uncontrolled CNS lesion.		The median PFS was - 2.8 months (95% CI, 2.3-3.3) in the mFOLFOX arm and - 2.1 months (95% CI, 1.1e3.1) in the mFOLFIRI arm (p Z 0.974 (logrank test); HR = 1.0 (95% CI, 0.7-1.5), p = 0.986. ORR and DCR were - 5.9% (95% CI, 0-12.4) and 66.7% (95% CI, 53.8-79.6), respectively, in the mFOLFOX arm and - 4.0% (95% CI, 0-9.4) and 64.0% (95% CI, 50.7-77.3), respectively, in the mFOLFIRI arm (p = 0.663 and p = 0.778, respectively. Adverse events: Adverse events of grade 3 were slightly more frequently observed in the mFOLFOX arm (55.4%) than in the mFOLFIRI arm (50.0%). Common grade 3/4 adverse events were neutropenia (25.0%) and AST/ALT elevation (16.1%) in the mFOLFOX arm and neutropenia (25.9%) and anaemia (17.2%) in the mFOLFIRI arm. No chemotherapy-related deaths	**Analysis:** Given the treatment assignment ratio of 1:1, 53 patients in each group should be evaluated in the study, and finally, 59 patients in each group were required considering that the dropout rate was 10%. mFOLFOX treated n=56, ITT n= 59 (three dropout before treatment); mFOLFIRI treated n=58, ITT n=59 (one dropout before treatment). **Notes:** Cochrane risk of bias tool (Rob)-1: 3 questions(s) were considered to be unclear risk of bias; 0 question(s) were considered to be high risk of bias. Overall risk of bias: Low. **Oxford CEBM Levels of Evidence (2011):** Randomized controlled trial (randomized phase 2 trial).

		were reported. **Author's Conclusion:** In conclusion, mFOLFIRI was not superior to mFOLFOX in unresectable locally advanced or metastatic BTC refractory to first-line gemcitabine and cisplatin combination. However, the clinical efficacy of mFOLFIRI was comparable with that of mFOLFOX. The adverse events were different. Therefore, irinotecanbased chemotherapy could be considered as a good alternative regimen to mFOLFOX at second-line BTC or the subsequent treatment after second-line mFOLFOX in BTC. A further study to evaluate the efficacy of irinotecan-based chemotherapy in the third-line setting of BTC is planned.	

Do-Youn Oh, M.D., Ph.D.1, Aiwu Ruth He, M.D., Ph.D.2, Shukui Qin, M.D.3, Li-Tzong Chen, M.D., Ph.D.4,5,6, Takuji Okusaka, M.D., Ph.D.7, Arndt Vogel, M.D.8, Jin Won Kim, M.D., Ph.D.9, Thatthan Suksomboon charoen, M.D.10, Myung Ah Lee, M.D., Ph.D.11, Masayuki Kitano, M.D., Ph.D.12, ... ,for the TOPAZ-1 Investigators*. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM. . . 2022

Population	Intervention / Comparison	Outcomes/Results	Methodical Notes

Evidence level: **Study type:** **Number of Patients:** **Recruiting Phase:** **Inclusion Criteria:** **Exclusion Criteria:**	**Intervention:** **Comparison:**	**Primary:** **Secondary:** **Results:** **Author's Conclusion:**	**Funding Sources:** **COI:** **Randomization:** **Blinding:** **Dropout Rate/ITT-Analysis:** **Notes:** Diese Studie wurde von der DKG entsprechend der GRADE Methodik bewertet.

Oh, D. Y. et al. Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naive patients with advanced biliary tract cancer: an open-label, single-centre, phase 2 study. Lancet Gastroenterol Hepatol. 7. 522-532. 2022			
Population	**Intervention / Comparison**	**Outcomes/Results**	**Methodical Notes**
Evidence level: **Study type:** **Number of Patients:** **Recruiting Phase:** **Inclusion Criteria:** **Exclusion Criteria:**	**Intervention:** **Comparison:**	**Primary:** **Secondary:** **Results:** **Author's Conclusion:**	**Funding Sources:** **COI:** **Randomization:** **Blinding:** **Dropout Rate/ITT-Analysis:** **Notes:** Diese Studie wurde von der DKG entsprechend der GRADE Methodik bewertet.

3.4. HCC Neu Bestrahlung

Inhalt: *7 Literaturstellen*

Literaturstelle	Evidenzlevel	Studientyp
Brunner, Thomas B 2021	3	Prospective, two-arm, non-randomized, study.
Comito, Tiziana 2022	3	Prospective, single-institution, randomized, controlled, unblinded, parallel-group phase III trial.
Eriguchi, T. 2021	2	Systematic review and META-Analysis of 6 observational studies.
Kim, T. H. 2021	2	Phase III investigator-initiated, randomized, single-center, open-label clinical trial.
Lee, J. 2020	3	Systematic review and META-Analysis of 11 observational studies.
Pan, Y. X. 2020	3	Systematic review and META-Analysis of 10 observational studies (non-randomized).
Rim, C. H. 2019	3	Systematic review and META-Analysis of 32 observational studies (non-randomized).

OXFORD (2011) - AMSTAR 2: Systematic Reviews: *4 Bewertung(en)*

Eriguchi, T. et al. Comparison of stereotactic body radiotherapy and radiofrequency ablation for hepatocellular carcinoma: Systematic review and meta-analysis of propensity score studies. Hepatol Res. 51. 813-822. 2021

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References
Evidence level: 2 **Overall confidence in the results of the review:** AMSTAR II critical appraisal tool for systematic reviews: One critical flaw (items 15), one non-critical flaws (item 10) Overall quality of evidence: low Oxford CEBM Levels of Evidence (2011): Systematic review of observational studies. **Study type:** Systematic review and META-Analysis of 6 observational studies. **Databases:** PubMed, the Cochrane database, EMBASE, and Web of Science. **Search period:** Until October 1, 2020. **Inclusion Criteria:** - studies using propensity score (PS) analysis that compared SBRT and RFA exclusively for HCC, with particular attention to the quality of matching, such as a	**Population:** HCC patinents **Intervention:** SBRT (stereotactic body radiotherapy) **Comparison:** RFA (radiofrequency ablation)	**Primary:** OS (overall survival), LC (local control), Toxicity **Secondary:** - **Results: Overall survival:** In total six retrospective studies, n=2107 patients. META 3 studies with matched BCLC factors, SBRT: n= 866, RFA n=1241. HR, 0.89; 95% CI, 0.74– 1.08; p = 0.24; I2 = 0%; p for heterogeneity, 0.56. Three additional studies (not BCLC matched): HR, 1.41; 95% CI, 1.21–1.65; p < 0.0001; I 2 = 0%; p for heterogeneity, 0.63. Considerable heterogeneity was observed in the HR of OS between BCLC-factor-matched and -unmatched studies (I2 = 92.6%; p for heterogeneity, 0.0002). **Local control:** Four retrospective studies, 1155 patients.	- Hara (2019) - Kim (2020) - Ueno (2020) - Feng (2016) - Wahl (2016) - Rajyaguru (2018)

propensity regarding BCLC staging; - Articles were published as full reports, brief reports, or conference abstracts, regardless of their primary end-point. Non-English reports were excluded from this study; - matching liver function (CP score or class), performance status, and tumor size, which are the components that determine BCLC staging. **Exclusion Criteria:** - Studies involving patients with metastatic liver tumors; - Studies using other ablative techniques such as microwave ablation, high-intensity focused ultrasound, laser therapy, or cryoablation; - reviews, letters, editorials, case reports and series, and laboratory studies.		META of three studies: Time to local recurrence of patients who were treated with SBRT was longer than those treated with RFA: HR, 0.39; 95% CI, 0.30–0.50; p < 0.00001; I2 = 0%; p for heterogeneity, 0.91. **Toxicity (Adverse events):** Three studies; The rates of grade 3 or higher toxicities ranged from 0% to 11%, which were not significantly different between RFA and SBRT. The uncompensated liver cirrhosis and liver-related deaths 12 months after treatment was significantly higher in the SBRT- HFRT in the report by Hara et al.7 However, the 3-year liver failure mortalities after propensity score matching were similar (p = 0.52). **Author's Conclusion:** When BCLC factors were properly adjusted, the results of the meta- analysis revealed equivalent OS and better LC for SBRT compared with RFA. Therefore, SBRT could be an alternative treatment option.		

Lee, J. et al. Comparisons between radiofrequency ablation and stereotactic body radiotherapy for liver malignancies: Meta-analyses and a systematic review. Radiother Oncol. 145. 63-70. 2020			
Evidence level/Study Types	**P - I - C**	**Outcomes/Results**	**Literature References**
Evidence level: 3 **Overall confidence in the results of the review:** AMSTAR II critical appraisal tool for systematic reviews: Two critical flaws (items 2 and 7), two non-critical flaws (items 10 and 12) Overall quality of evidence: critically low **Oxford CEBM Levels of Evidence (2011):** Systematic review of observational studies. Downgraded one level due to "Critically low" quality of the AMSTAR appraisal (no protocol registered and excluded studies not listed). **Study type:** Systematic review	**Population:** Intrahepatic malignancies including hepatocellular carcinoma or liver metastases **Intervention:** RFA OR radiofrequency **Comparison:** SBRT OR stereotactic	**Primary:** local control (LC) and overall survival (OS) **Secondary:** - **Results:** 11 studies with 2238 patients were included in the meta-analysis, comprising 1329 and 909 patients who underwent RFA and SBRT, respectively. Eight studies were for treating early hepatocellular carcinomas (HCCs) and three for liver metastases. Most studies performed propensity score matching (PSM) or statistical comparisons to show no significant difference between arms. **Overall survival:** Among the 10 studies that provided survival comparisons, none showed statistically significant differences except one. Pooled analysis of overall survival (OS) in HCC studies showed an odds ratio of 1.43 (95% CI: 1.05–1.95, p = 0.023), favoring RFA. Among the two liver metastases studies with comparative	- Wahl DR, 2016, J Clin Oncol. - Rajyaguru DJ, 2018, J Clin Oncol. - Ahuja CKY, 2014, CardioVasc Interventional Radiol (conference abstract). - Shiozawa K, 2015 World J Gastroenterol. - Duan XZT, 2016, Hepatology (conference abstract). - Feng MU-S, 2016, J Clin Oncol (conference abstract). - Hara KTA, 2018 Hepatology (conference

and META-Analysis of 11 observational studies. **Databases:** Medline and EMBASE **Search period:** no restrictions **Inclusion Criteria:** (1) clinical trials treating intrahepatic malignancies including hepatocellular carcinoma or liver metastases; (2) provision of at least one of the primary endpoints; and (3) treatment arms, each including >5 patients with intrahepatic malignancies. **Exclusion Criteria:** - Editorials, letters, reviews, case reports, and non-human studies were excluded. - Studies which were not clinical trials or duplicated studies among databases		survival data, no significant difference was observed. **Local control: (LC)** Including HCCs and liver metastases studies, the pooled two-year LC rate was higher in the SBRT arm (83.8%, 95% CI: 77.6–88.4) than that in the RFA arm (71.8%, 95% CI: 61.5–80.2) ($p = 0.024$). Among studies on liver metastases, the pooled two-year LC rate was higher in the SBRT arm (83.6% vs.60.0%, $p < 0.001$). No significant difference was found between arms in HCC studies (SBRT vs. RFA: 84.5 vs. 79.5% $p = 0.431$). **Adverse events:** Complications related to treatment were available in nine studies, with severe toxicity rates (grade 3) ranging from 0 to 12% in both arms. The rates of severe complications were mostly lower than 5% in both arms among the included studies. Six studies performed statistical comparisons of severe complications, none of which showed statistically significant differences. **Author's Conclusion:** Summarizing the present study, LC in the present study was equivalent between RFA and SBRT for HCC and better for SBRT for the treatment of liver metastases. Both	abstract). - Kim N, 2019, Radiother Oncol. - Stintzing S, 2013, Acta Oncol. - Vigano L, 2018, World J Surg. - Jackson WC, 2018, Int J Radiat Biol Phys.	

		modalities were comparably feasible regarding toxicities. For HCC, the efficacy of SBRT might be better especially for tumors larger than 2–3 cm, as shown in the literature review. RFA was associated with better survival for treating HCC, but the discrepancy between LC and overall survival requires further investigation, as they are both local modalities showing equivalent efficacy. Future randomized trials can help to identify the discrepancy, and suitable indications for each modality.		

Pan, Y. X. et al. Stereotactic Body Radiotherapy vs. Radiofrequency Ablation in the Treatment of Hepatocellular Carcinoma: A Meta-Analysis. Front Oncol. 10. 1639. 2020

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	
Evidence level: 3 **Overall confidence in the results of the review:** AMSTAR II critical appraisal tool for systematic reviews: Two critical flaws (items 2 and 7), three non-critical flaws (item 6, 10 and 12) Overall quality of evidence: critically low Oxford CEBM Levels of	**Population:** Diagnosed primary liver cancer definitively and patients diagnosed with HCC based on pathological evidence from fine needle aspiration (FNA) or in the absence of biopsy evidence, based on imaging techniques including contrast-enhanced ultrasonography (CEUS), computed tomography (CT), and magnetic resonance imaging (MRI) companied with alphafetoprotein elevation. **Intervention:** SBRT	**Primary:** Local progression (LP) control and overall survival (OS). LP was defined as the recurrence of lesion in the treatment area by imaging studies. And LP time was the period from the initial treatment to the discovery of LP or last follow-up. The OS was defined the period from the date of initial treatment of the HCC to the date of death related to any cause or last follow-up. **Secondary:** -	- Sapisochin G, 2017, J Hepatol. - Wahl DR, 2016, J Clin Oncol. - Parikh ND, 2018 J Med Imaging Radiat Oncol. - Wahl D, 2014, Int J Radiat Oncol Biol Phys.	

Evidence (2011): Systematic review of observational studies. Downgraded one level due to "Critically low" quality of the AMSTAR II appraisal (no protocol registered and excluded studies not listed). **Study type:** Systematic review and META-Analysis of 10 observational studies (non-randomized). **Databases:** PubMed Central, Embase, Cochrane Library, and Google Scholar **Search period:** until August 26, 2019. **Inclusion Criteria:** - humans and English-language studies; - no evidence of invasion into the major portal/hepatic vein branches or extrahepatic metastasis based on radiologic imaging; - patients without previous treatment of transcatheter arterial chemoembolization (TACE), surgery, chemotherapy, or other antitumor treatment;	**Comparison:** RFA	**Results:** 2,732 patients from the 10 included studies, 859 patients were classified into the SBRT group, and the rest of the 1,873 patients were classified into the RFA group. **Local Progression Rates (LP rates):** Six studies; SBRT vs RFA 1- year LP rates OR 0.47, 95% CI 0.26–0.83, P = 0.010; χ 2 = 2.93, I2 = 0% (5 studies). 2-year LP rate OR 0.67, 95% CI 0.43–1.05, P = 0.080, χ2 = 0.33, I2 = 0% (4 studies) 3-year LP rates OR 0.55, 95% CI 0.37–0.81, P = 0.003, χ2 = 2.66,I2 = 0% (4 studies). **Overall survival (OS):** Nine studies with 2,700 patients compared OS rates of SBRT group with RFA group. 1-year OS OR 1.38, 95% CI 1.00–1.93, P = 0.050; I2= 33% (8 studies). 2- year OS OR 1.57, 95% CI 1.23–2.00, P < 0.0003; I2= 24% (7 studies). 3-years OS OR 1.44, 95% CI 0.90–2.33, P = 0.130; I2= 76% (6 studies). 5-year OR 1.35, 95% CI 0.81–2.26, P = 0.250; I2= 77% (4 studies).	- Rajyaguru DJ, 2018, J Clin Oncol. - Shiozawa K, 2015, World J Gastroenterol. - Mohamed M, 2016, Adv Radiat Oncol. - Berger NG, 2017, J Surg Oncol. - Hara K, 2019, Hepatology. - Duon X, 2016, Hepatology.	

- documented indications for SBRT and RFA clearly; - either randomized controlled trials (RCTs) or retrospective studies were candidates; - patients of two groups with comparable basic clinical characters; and - studies with outcome information regarding LP rates, OS rates, and/or transplant rates. **Exclusion Criteria:** - studies that did not report original data, including abstracts, case reports, expert opinions, editorials, reviews, or letters; - either group in the studies or combined other therapies; - studies based on the same cohort.		**Prognosis for Treatment Allocation:** The treatment allocation was not a prognostic factor for LP (HR 0.72, 95% IC 0.42–1.25, P = 0.240, three studies). However, RFA group was more favorable than SBRT group for OS benefits (HR 1.43, 95% IC 1.24–1.64, P < 0.00001, five studies). **Transplant and Post-transplant Pathological Necrosis Rate:** There were no significant differences in transplant rate and post-transplant pathological necrosis rate for both SBRT and RFA (OR 0.65, 95% CI 0.24–1.79, P = 0.040; and OR 0.46, 95% CI 0.13–1.63, P = 0.230, respectively. **Author's Conclusion:** In sum, our meta-analysis shows that SBRT provided better local control than RFA, and it could be used as a potential alternative local control treatment for HCC.		

Rim, C. H. et al. Clinical feasibility and efficacy of stereotactic body radiotherapy for hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. Radiother Oncol. 131. 135-144. 2019

Evidence level/Study Types	P - I - C	Outcomes/Results	Literature References	

Evidence level: 3 **Overall confidence in the results of the review:** AMSTAR II critical appraisal tool for systematic reviews: Two critical flaws (items 2 and 7), three non-critical flaws (items 6, 10 and 12) Overall quality of evidence: critically low **Oxford CEBM Levels of Evidence (2011):** Systematic review of observational (non-randomized) studies. Downgraded one level due to "Critically low" quality of the AMSTAR appraisal (no protocol registered and excluded studies not listed) **Study type:** Systematic review and META-Analysis of 32 observational studies (non-randomized). **Databases:** PubMed, Medline, Embase, and Cochrane Library database **Search period:** Until April 23, 2018 **Inclusion Criteria:** - not use any	**Population:** HCC patients **Intervention:** SBRT or stereotactic ablative radiotherapy (SABR) **Comparison:** -	**Primary:** Survival or tumor control rate **Secondary:** Complications of grade 3. **Results:** 32 studies comprising 33 cohorts, consisting of 1950 patients. **Overall survival (OS):** 1-year OS 72.6% (95% CI: 65.7–78.6) 2-year OS 57.8% (95% CI: 50.9–64.4) 3-year OS 48.3% (95% CI: 40.3–56.5); all significant heterogeneity. In subgroup comparisons, differences between subgroups categorized by **tumor size** (median value of 5 cm) were statistically significant for 1-year OS rate ($p < 0.001$) and 2-year OS rate ($p = 0.020$), and tended to be significant for 3- year OS rate ($p = 0.070$). For subgroup comparisons categorized by **radiation dose** (median EQD2 estimates of 80 Gy10), no statistically significant difference was found among all three comparisons regarding OS. **LC** 1-year LC, 85.7% (95% CI: 80.1–90.0) 2-year LC, 83.6% (95% CI: 77.4–88.3) 3-year LC, 83.9% (95% CI: 77.6–88.6); all significant heterogeneity. In the subgroup comparisons regarding **tumor size** (median value of 5 cm), the differences were statistically	Shiozawa K 2015. Huertas A 2015. Yoon SM 2013. Jeong Y 2018. Bibault JE 2013. Kubo K 2018. Sanuki N 2014. Sanuki N-2 2014. Andolino DL 2011. Jang WI 2013. Yamashita H 2014. Kwon JH 2010. Ibarra RA 2012. Feng M 2018. Bujold A 2013.	

language restriction - clinical trials, including retrospective or prospective studies; - inclusion of at least 10 patients with HCC treated with SBRT or SABR; - SBRT performed in - provision of at least one subject from both survival and local control. **Exclusion Criteria:** - exclude duplicated studies, conference abstracts, reviews, letters, editorials, case reports, lab studies, and studies with irrelevant subjects. - multiple studies from one institution (only one included).		significant for 1-year, 2-year, and 3-year LC rates ($p < 0.001$, 0.001, and 0.001, respectively). In the subgroup comparisons regarding **radiation dose** (median EQD2 estimates of 80 Gy10), the difference was marginally significant for 1-year LC rate ($p = 0.071$), and not significant for 2- and 3-year LC rates. **Adverse events:** The most commonly reported complications of grade 3 were GI or hepatic toxicities. GI toxicities: the pooled rate was 3.9% (95% CI: 2.6–5.6). Hepatic toxicities: The pooled rate was 4.7% (95% CI: 3.4–6.5). <u>META-regression:</u> Child-Pugh class was significantly correlated with hepatic complication of grade 3 in meta-regression analysis ($p = 0.013$). **Author's Conclusion:** The present study reported pooled results of oncologic outcomes based on the integration of information from a large number of trials, providing support for the clinical efficacy and feasibility of SBRT for HCC. Both OS and LC were affected by tumor size, and radiation dose marginally affected LC. LC rates for small HCCs were excellent, and moderate efficacy was shown in treatment of tumors 5 cm. Rates of serious complications were low, either hepatic or GI, suggesting the feasibility of SBRT for HCC. However, liver function should be considered to find patients eligible for SBRT in	Lo C.-H. 2017. Scorsetti M 2015. Kim JW 2016. Hasan S 2017. Madhavan R 2017. Zhang T 2018. Que J 2016. Hijazi H 2016. Gkika E 2018. Kim M 2017. Uemoto K 2018. Lam MHC 2017. Sapir E 2018. Moon DH 2018. Guarneri A 2016. Weiner AA 2016. Baumann	

		order to avoid severe hepatic toxicity. Randomized trials are warranted to prove the clinical benefit of SBRT for HCC, and combination use with systemic treatment is another projected subject of future research.	BC 2018. Hanazawa H 2017.	

Cochrane Risk of Bias Tool 1 (RCT): *3 Bewertung(en)*

Brunner, Thomas B. Efficacy of Stereotactic Body Radiotherapy in Patients With Hepatocellular Carcinoma Not Suitable for Transarterial Chemoembolization (HERACLES: HEpatocellular Carcinoma Stereotactic RAdiotherapy CLinical Efficacy Study). Frontiers in oncology. 11. . 2021			
Population	**Intervention / Comparison**	**Outcomes/Results**	**Methodical Notes**
Evidence level: 3 **Study type:** Prospective, two-arm, non-randomized, study. **Number of Patients:** 39 HCC patients (n= 19 allocated to TACE, n=20 allocated to SBRT) **Recruiting Phase:** The active recruitment time was 12 months (06/2016 and 06/2017). **Inclusion Criteria:** - Age ≥ 18 years, male and female - Histologically or cytologically confirmed hepatocellular carcinoma OR diagnosis made with characteristic enhancement in 4-Phase CT or MRI corresponding to AASLD- / EASL guidelines in cirrhotic patients. - Discussion in a routine multidisciplinary tumour board - Understanding of procedure, significance and consequences	**Intervention:** SBRT **Comparison:** TACE	**Primary:** Feasibility of SBRT in everyday clinical practice **Secondary:** - Toxicity according to the NCI-CTCAE v4.0 for adverse events, - health related quality of life (QOL), - incidence of local progression (LP) (according to mRECIST), - overall survival (OS) and - progression free survival (PFS) For QOL: Patients treated with SBRT filled in the EORTC QLQ-C30 and QLQ C29 at the first treatment, 4 weeks after the last treatment and at the second follow up (3 months later). For the patients treated with TACE the QLQ assessment was before and after the treatment. **Results:** TACE n= 19, SBRT n= 18. The median follow-up was 31 months.	**Funding Sources:** This study was funded by the German Consortium for Translational Cancer Research (Deutsches Konsortium für Translationale Krebsforschung, DKTK)-Partner Site Freiburg. DB was funded by the Berta-Ottenstein-Programme for Advanced Clinician Scientists, Faculty of Medicine, University of Freiburg. **COI:** DB: consulting and advisory: Bayer Healthcare, Boston Scientific; teaching and speaking fees: Falk Foundation. MS: consulting and advisory: Bayer Healthcare; teaching and speaking fees: L.W. Gore, Falk Foundation. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. **Randomization:** Patients received either TACE or SBRT according to the decision of the institutional HCC tumor board,

of the study - signed informed consent <u>specific for SBRT:</u> - Patients unsuitable for surgery, TACE*, RFA, or alcohol ablation - bilirubin has to be < 4 x the upper limit of normal, AST or ALT < 6 x the upper limit of normal, international normalized ratio < 1.5 except if patients are on oral anticoagulation, haemoglobin≥ 90 g/L, platelets ≥ 50 x 109/L, and neutrophils ≥ 1.0 x 109/L <u>specific for TACE:</u> - Patients suitable for TACE - bilirubin has to be < 6 x the upper limit of normal, international normalized ratio < 1.5 except if patients are on oral anticoagulation, haemoglobin≥ 90 g/L, platelets ≥ 50 x 109/L, and neutrophils ≥ 1.0 x 109/L **Exclusion Criteria:** None of the following criteria must be present at the time of registration: - Child-Turcotte-Pugh (CTP) C liver score		**Quality of Life (QOL):** The QOL remained stable before and after treatment and was comparable in both treatment groups. **Toxicity/Adverse events:** Five patients developed grade ≥ 3 toxicities in the TACE group and 3 in the SBRT group. **LP, PFS and OS:** The cumulative incidence of LP after 1-, 2- and 3-years was 6, 6, 6% in the SBRT group and 28, 39, and 65% in the TACE group (p = 0.02). The <u>median PFS</u> was 4 months in the SBRT group and 11 months in the TACE group (HR: 2.172, 95% CI 0.988– 4.775, p = 0.05) which remained also significant on multivariate analysis (HR: 2.855, 95% CI: 1.227–6.644, p = 0.02). Patients with - a BCLC stage A (HR: 0.208, 95% CI: 0.055–0.787, p = 0.02), - with multiple HCC (HR: 2.759, 95% CI: 1.207–6.3006, p = 0.02) as well as patients with - prior treatments (HR: 2.693, 95% CI: 1.199–6.046, p = 0.02) had a better PFS. The <u>1- and 2- years OS rates</u> were 84%	taking into account the standard treatment algorithm. TACE was offered in patients with localized disease and/or with contraindications for resection, transplantation or RFA. For patients where TACE or systemic treatment were not deemed suitable either due to exclusion criteria or for any other reason such as patient preference, SBRT was offered as an alternative. **Blinding:** n.s. **Dropout Rate/ITT-Analysis:** 2 patients in the SBRT group did not receive allocated intervention because of tumor progression. No patients lost to follow-up. **Notes: Oxford CEBM Levels of Evidence (2011):** Non-randomized controlled trial. EL 3 High risk of bias due to missing randomization (selection bias). The baseline characteristics of the patients in the treatment groups differs significantly, probably due to the used allocation method. From methodological point of view, this has to be considered during interpreting the results. From clinical point of view this might be reasonable to offer the patients the best suitable and possible treatment. As a consequence we refrain from further downgrading.

- Hepatic encephalopathy more than Grade 1 according to Child Pugh criteria (Appendix 3) - Active hepatitis - Gastric, duodenal or variceal bleed within 2 months of registration - Prior radiotherapy of the region to be treated - For female patients: Pregnancy, planned pregnancy		and 47% in the TACE group and 44% and 39% in the SBRT group (p = 0.20). Patients with a - higher CP score (HR 3.968,95% CI: 1.419–11.096, p = 0.01) - larger tumors (HR: 3.214, 95% CI: 1.355–7.624, p = 0.01) and - PVT (HR: 3.107, 95% CI: 1.116–8.648 p = 0.03) had a worse OS, which remained significant on multivariate analysis. **Author's Conclusion:** This is the first published trial evaluating TACE and SBRT in a prospective manner, showing that SBRT is a well-tolerated locally effective treatment that does not impair the quality of life of multi-morbid patients, and could be considered as an alternative in carefully selected patients with contraindications for TACE.	

Comito, Tiziana. Stereotactic Radiotherapy after Incomplete Transarterial (Chemo-) Embolization (TAE\TACE) versus Exclusive TAE or TACE for Treatment of Inoperable HCC: A Phase III Trial (NCT02323360). Current oncology (Toronto, Ont.). 29. . 2022

Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 3 **Study type:** Prospective, single-institution, randomized, controlled, unblinded, parallel-	**Intervention:** SBRT following the incomplete response of unresectable HCC previously treated with	**Primary:** Control of local disease, LC **Secondary:** Overall Survival, OS; Distant Recurrence-Free Survival,	**Funding Sources:** This research received no external funding. **COI:** : Related To The Current Work, The authors declare no

group phase III trial. **Number of Patients:** Patients with BCLC A-B disease (n=21 SBRT, n=19 TAE/TACE (15 patients received bland embolization, and 4 received epirubicin-based TACE). **Recruiting Phase:** November 2014 to September 2019 **Inclusion Criteria:** Adult patients with Karnofsky Performance Status (KPS) >70% were eligible if they were 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. **Exclusion Criteria:** - Concurrent malignancy, - uncontrolled infection, - severe anomalies in blood tests,	one TAE/TACE cycle. **Comparison:** A second course of TAE/TACE following the incomplete response of unresectable HCC previously treated with one TAE/TACE cycle.	DRFS; and Progression-Free Survival, PFS. **Results:** The median follow-up duration was 20 (range 3–56) months. **Local control:** Median LC was 12 months (CI95% 7–20) in the overall population. 1- year LC rate: 56% 2-year LC rate: 36% The use of SBRT compared to TAE/TACE: HR: 0.15 [CI95% 0.04–0.4]. Corresponding to a 1-year LC of 84% vs. 23%. No other clinical- or treatment-related variables were correlated with the incidence of local failure. **Progression free survival:** Median PFS was 6 (CI95% 4–9) months; 1- and 2-year PFS was 26% and 11%. 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]). In the TAE arm, PFS was 13% and 6% at 1 and 2 years, respectively.	conflict of interest. **Randomization:** A computer-generated minimization program that incorporates a random element was used. **Blinding:** - **Dropout Rate/ITT-Analysis:** The sample size calculation was based on the assumption that at least 50 patients were needed for randomization (25 per arm, 50% randomization rate in both arms) to achieve 80% power to detect an LC Hazard Ratio (HR) of 0.18 (corresponding to a 45% difference at the analysis time, 85% vs. 40% in favor of SBRT versus TAE/TACE) with a 5% two-sided type I error. This corresponded to 18 events following study initiation: as of 23rd September 2019, enrollment was prematurely stopped before planned target accrual was reached (n = 40) due to the early achievement of the pre-specified planned number of event. **Notes:** Cochrane risk of bias tool (Rob)-1: 3 questions(s) were considered to be unclear risk of bias; 0 question(s) were considered to be high risk of

- previous abdominal irradiation and - Grade ≥3 hemorrhagic complications within 4 weeks of enrollment in the study.		**Overall survival:** Median OS was 30 (CI95% 20–36) months, corresponding to a 1-year and 2-year OS of 86% and 62%, respectively. 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. In the univariate analysis, OS was significantly impacted by Child–Pugh A liver disease (median 31 versus 17 months, p = 0.022; HR 0.22 [CI95% 0.05–0.80]) and prior aggressive locoregional management including surgery and/or RFA/PEI (median 47 versus 22 months, p = 0.007; HR 0.28 [CI95% 0.11–0.70]). **Adverse events:** No grade >3 toxicity was observed in any treatment arm. **Author's Conclusion:** In this phase III open trial, patients affected by inoperable HCC experiencing an incomplete response following ≥1 cycle of TAE/TACE, SBRT was correlated with significantly higher LC rates as compared to rechallenge with TAE/TACE. This was correlated	bias. Overall risk of bias: Low. **Oxford CEBM Levels of Evidence (2011):** Randomized controlled trial. The presented results (table 2, figure 3 and results) are not congruent in all points. This reduces our confidence in the results, which is why we chose to downgrade the quality of the evidence of one level to EL 3.

		with extended PFS in the SBRT arm, though no difference was found in the onset of new lesions outside the target tumor. Although no significant OS advantage was found for SBRT over TAE/TACE, an aggressive locoregional schedule may improve outcomes in selected patients.	

Kim, T. H. et al. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: a randomized phase III trial. Journal of hepatology. 74. 603?612. 2021

Population	Intervention / Comparison	Outcomes/Results	Methodical Notes
Evidence level: 2 **Study type:** Phase III investigator-initiated, randomized, single-center, open-label clinical trial. **Number of Patients:** 144 patients were randomly assigned (n=72 PBT arm, n=72 RFA arm) from the National Cancer Center (NCC), Goyang, Republic of Korea. **Recruiting Phase:** December 2013 and December 2017, **Inclusion Criteria:** - HCC	**Intervention:** PBT **Comparison:** RFA	**Primary:** 2-year local progression-free survival (LPFS). Planned clinical, laboratory, and tumor assessment via contrast-enhanced multiphasic CT or MRI was performed within 2 weeks before each treatment, at the first month after the completion of RFA or PBT, every 3 months for the following 2 years, and every 6 months thereafter. **Secondary:** Progression-free survival (PFS), overall survival (OS) safety, defined as the presentation of adverse events (AEs) related to the treatments that were assessed. **Results:** The median follow-up duration was 51.6 months (90% CI 45.6–59.5) (IQR 39.3–67.8) in the PBT arm and 50.7 months	**Funding Sources:** This study was supported by the National Cancer Center Grant, Korea (NCC 1810271, 1810031 and 1710030). The funding source had no role in the study design, data curation, or the analysis and interpretation of data. **COI:** see publication **Randomization:** Eligible patients were randomly assigned (1:1) to the PBT arm or RFA arm with stratification according to the Child-Pugh classification (A vs. B7) and tumor stage (American Joint Committee on Cancer [AJCC] 7th edition stage I–II vs. III). After randomization to each treatment arm, if the assigned method was not technically feasible, the patients were allowed to be

diagnosis was confirmed either histologically or clinically according to the Korean Liver Cancer Study Group and NCC Korea guidelines; - presence of recurrent or residual HCC lesions without vascular invasion after other treatment; - the largest diameter and number of target lesion(s) were - no history of prior radiotherapy to targeted lesion(s); - no evidence of extrahepatic metastasis; - Child-Pugh score - Eastern Cooperative Oncology Group performance status - age >−18 years; - adequate bone marrow and liver function. All patients were unresectable or unwilling to undergo resection. **Exclusion Criteria:** see inclusion criteria		(90% CI 45.8–57.7) (IQR 41.4–67.4) in the RFA arm. **2-year LPFS:** In the PP population, the 2-year LPFS rate with PBT (n = 80) vs. RFA (n = 56) was 94.8% vs. 83.9%, a difference of 10.9 percentage points (90% CI 1.8–20.0; p ITT population, the 2-year LPFS rate with PBT vs. RFA was 92.8% vs. 83.2%, a difference of 9.6 percentage points (90% CI 0.7–18.4; p **Overall survival:** The median OS value was not reached in both arms and both populations. In the PP and ITT populations, the 2-year OS rates were 88.8% and 91.7% in the PBT arm, and 92.9% and 90.3% in the RFA arm, respectively; the HRs of the OS rate between the PBT and RFA arms were not different (HR 1.19; 95% CI 0.62–2.27; HR 1.07; 95% CI 0.58–1.98, respectively). **Adverse events:** The most common adverse events were radiation pneumonitis (32.5%) and decreased leukocyte counts (23.8%) for PBT and increased alanine aminotransferase levels (96.4%) and abdominal pain (30.4%) for RFA. No	treated with the other method. **Blinding:** Patients and all investigators were unmasked to the treatment assignment. **Dropout Rate/ITT-Analysis:** ITT n=72 for each arm; per protocol analysis RFA arm n=56, PBT arm n=80. PBT arm: 6 (8.3%) patients crossed over to the RFA arm and 5 patients received another treatment. RFA arm: 19 (26.4%) patients crossed over to the PBT arm and 3 received another treatment. **Notes:** Cochrane risk of bias tool (Rob)-1: 3 questions(s) were considered to be unclear risk of bias; 0 question(s) were considered to be high risk of bias. Overall risk of bias: Low. Oxford CEBM Levels of Evidence (2011): Randomized controlled trial.

		Grade 4 adverse events or mortality were noted. **Author's Conclusion:** In conclusion, this prospective randomized study demonstrated that PBT is associated with LPFS rates that are comparable to those observed for RFA in patients with rHCC with	