Update richtlijn Galweg- en galblaascarcinoom (7 modules)

april 2024

INITIATIEF
Nederlandse Vereniging voor Heelkunde

IN SAMENWERKING MET
Nederlandse Internisten Vereniging
Nederlandse Vereniging voor Radiologie
Nederlandse Vereniging van Maag-Darm-Leverartsen
Nederlandse Vereniging voor Pathologie
Verpleegkundigen en Verzorgenden Nederland
Nederlandse Federatie van Kankerpatiëntenorganisaties | Patiëntenplatform Zeldzame Kankers

MET ONDERSTEUNING VAN
Kennisinstituut van de Federatie Medisch Specialisten

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

Colofon

UPDATE RICHTLIJN GALWEG- EN GALBLAASCARCINOOM (7 MODULES)

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Inhoudsopgave

Samenstelling van de werkgroep

Werkgroep

- Dr. B. (Bas) Groot Koerkamp, Chirurg/ Epidemioloog, Erasmus MC, Rotterdam, NVvH (voorzitter)
- Dr. J.I. (Joris) Erdmann, Chirurg, Amsterdam UMC, Amsterdam, NVvH
- Dr. P.R. (Philip) de Reuver, Chirurg, Radboudumc, Nijmegen, NVvH
- Dr. M.T. (Marieke) de Boer, Chirurg, UMCG, Groningen, NVvH ((tot mei 2022)
- Dr. F.J.H. (Frederik) Hoogwater, Chirurg, UMCG, Groningen, NVvH (vanaf mei 2022)
- Dr. H.J. (Heinz-Josef) Klümpen, Internist-oncoloog, Amsterdam UMC, Amsterdam, NIV
- Dr. N. (Nadia) Haj Mohammad, Internist-oncoloog, UMC Utrecht, Utrecht, NIV
- Drs. F.E.J.A. (François) Willemsen, Abdominaal radioloog, Erasmus MC, NVvR
- Prof. dr. O.M. (Otto) van Delden, interventieradioloog, Amsterdam UMC, Amsterdam, NVvR
- Dr. L.M.J.W. van Driel, maag-darm-leverarts, Erasmus MC, Rotterdam, NVMDL
- Prof. dr. J. (Joanne) Verheij, klinisch patholoog, Amsterdam UMC, Amsterdam, NVVP
- Dr. R.S. (Chella) van der Post, patholoog, Radboudumc, Nijmegen, NVVP (vanaf februari 2022)
- C. (Chulja) Pek, Verpleegkundig specialist, Erasmus MC, Rotterdam, V&VN
- Drs. M.A. (Marga) Schrieks, Projectleider Patiëntenplatform Zeldzame Kankers, NFK
- A. (Anke) Bode MSc, Patiëntvertegenwoordiger, NFK (tot april 2023)
- Drs. A.C. (Christine) Weenink, Patiëntvertegenwoordiger/huisarts, NFK (vanaf april 2023)

Met dank aan

- M. (Mike) van Dooren, arts-onderzoeker, Radboudumc, Nijmegen

Met ondersteuning van

- Drs. M. Oerbekke, Adviseur, Kennisinstituut van de Federatie Medisch Specialisten
- Dr. N. Elbert, Adviseur, Kennisinstituut van de Federatie Medisch Specialisten
- Dr. L.J.M. Oostendorp, Senior adviseur, Kennisinstituut van de Federatie Medisch Specialisten

Verantwoording

Autorisatie en geldigheid

Autorisatiedatum:	[verwachte datum rond mei 2024]
Geautoriseerd door:	Nederlandse Vereniging voor Heelkunde, initiatiefnemer Nederlandse Internisten Vereniging Nederlandse Vereniging voor Radiologie Nederlandse Vereniging van Maag-Darm-Leverartsen Nederlandse Vereniging voor Pathologie Verpleegkundigen en Verzorgenden Nederland Nederlandse Federatie van Kankerpatiëntenorganisaties | Patiëntenplatform Zeldzame Kankers

Overzicht modules

Tranche 1 (deze modules zijn in 2023 geautoriseerd)

Hoofdstuk	Nr	Moduletitel	Vorm
Diagnostiek	1	Meerwaarde PET bij biliare tumoren	Nieuw ontwikkeld
Behandeling	2	Preoperatieve galwegdrainage	Nieuw ontwikkeld
Pathologie	3	Verslag en aanvraag pathologie	Update van bestaande module
Communicatie en besluitvorming	4	Communicatie en besluitvorming	Nieuw ontwikkeld
Nazorg	5	Nazorg en nacontrole	Update van bestaande module

Tranche 2 (huidige autorisatieronde)

Hoofdstuk		Moduletitel	Vorm
Diagnostiek	6	Cross-sectionele beeldvorming	Update van bestaande module
Behandeling	7	Locoregionale behandeling met TACE of SIRT voor iCCA	Nieuw ontwikkeld
Behandeling	8	Preoperatieve vena porta embolisatie	Update van bestaande module
Behandeling	9	Indicatie resectie	Update van bestaande module
Behandeling	10	Adjuvante systemische behandeling	Update van bestaande module
Behandeling	11	Palliatieve systemische behandeling in de 1e lijn	Update van bestaande module
Behandeling	12	Palliatieve systemische behandeling na de 1e lijn	Update van bestaande module

Algemene gegevens

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

Samenstelling werkgroep

Voor het ontwikkelen van de richtlijnmodule is in 2020 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen (zie hiervoor de Samenstelling van de werkgroep) die betrokken zijn bij de zorg voor patiënten met galweg- of galblaascarcinoom.

Belangenverklaringen
De Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden hebben schriftelijk verklaard of zij in de laatste drie jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatiemanagement) hebben gehad. Gedurende de ontwikkeling of herziening van een module worden wijzigingen in belangen aan de voorzitter doorgegeven. De belangenverklaring wordt opnieuw bevestigd tijdens de commentaarfase.

Een overzicht van de belangen van werkgroepleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten.

Werkgroeplid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Groot Koerkamp	Chirurg en epidemioloog, Erasmus MC	Onbetaald: * secretaris wetenschappelijke commisssie van de Ducth Pancreatic Cancer Group (DPCG) * bestuurslid van de Dutch Hepatocellular and Cholangiocarcinoma Group (DHCG) * Lid van de audit commissie van de Nederlandse Vereniging voor Heelkunden (NVvH) * Voorzitter van de werkgroep cholangiocarcinoom van de DHCG * Lid van de wetenschappelijke commissie van de DHCG	<u>Intellectuele belangen en reputatie</u> Expertise op gebied van intra-arteriele chemotherapie. Ik ben PI vna een door KWF gefinancierde klinische studie van intra-arteriele chemotherapie voor niet-resectabel intrathepatisch cholangiocarcinoom	Geen restricties (in deze herziening komt het onderwerp Hepatic Arterial Infusion niet aan de orde)
Erdmann	Chirurg, Amsterdam UMC	Geen	Geen	Geen restricties
De Reuver	Chirurg gastro-enterologische chirurgie, Radboudumc, Nijmegen	Geen	<u>Extern gefinancierd onderzoek</u> PI van onderzoek naar Galblaascarcinoom, in 2017 gefinancieerd door Stichting ADP. Stichting heeft geen belang in het advies of de richtlijn.	Geen restricties
De Boer	Chirurg UMCG afdeling chirurgie, HPB chirurgie en levertransplantatie	Geen	Geen	Geen restricties
Hoogwater	Chirurg, Hepato-Pancreato-Biliaire Chirurgie en	* Bestuurslid - Dutch Hepatocellular & Cholangiocarcinoma	Geen	Geen restricties

	Levertransplantatie, Universitair Medisch Centrum Groningen	Group (DHCG), onbetaald * Commissielid - Continue Professionele Educatie van de NVvH, onbetaald * Lid - Wetendchappelijke Commissie Dutch Hepato Biliary Audit (DHBA), vacatiegeld * Bestuurslid Nederlandse Vereniging Chirurgische Oncologie (NVCO), onbetaald		
Klümpen	Internist-oncoloog in Amsterdam UMC	* Subdomain leader for biliary tract cancer EURACAN (onbetaald) * Lid wetenschappelijke commissie van de DHCG (onbetaald) * Dutch representative for European Cooperation in Science and Technology COST (biliary tract cancer) grant by HORIZON 2020 (onbetaald, wel worden reizen vergoed die door COST georganiseerd worden) * Member of European Network for the Study of Cholangiocarcinoma ENSCCA (onbetaald) * Member international billary tract cancer consortium IBTCC (onbetaald)	<u>Extern gefinancierd onderzoek</u> KWF financieert de ACTICCA studie en PUMP 2 studie, deze studies zijn gesloten voor inclusie Het Amsterdam UMC met mij als lokale PI doet mee en heeft meegedaan aan studies voor galweg en galblaascarcinoom: * TAS-120 studie van TAIHO (fase I/II) * SIRCCA studie van SIRTEX (fase III, is vroegtijdig gestopt) * KEYNOTE 966 studie van MSD (fase III studie)	Geen restricties tenzij een van de middelen uit het extern gefinancierd onderzoek toch aan de orde komt in deze herziening. In dat geval volgt uitsluiting van de formulering van de aanbevelingen over de middelen in de betreffende trials. TAS-120: futibatinib (TAIHO) SIRCCA: selective internal radiotherapy SIRT met 90-Y microspheres i.c.m. chemotherapie (SIRTEX) KEYNOTE-966: pembrolizumab (MSD)
Haj Mohammad	Internist-oncoloog, Universitair Medisch Centrum Utrecht	* Penningmeester Dutch Upper GI Cancer (DUCG), onbetaald * Lid Wetenschappelijke raad DHCG, onbetaald * Member of European Network for the Study of	<u>Extern gefinancierd onderzoek</u> * Merck – MK 966 gemetastaseerd BTC fase 3, gem cis + placebo vs gem cis + pembrolizumab (lokale PI) * Incyte – FIGHT-302: FGFR fusie, fase 3 gerandomiseerd gem	Bij aanvang van het project waren geen restricties geformuleerd. Bij het herbevestigen van belangen werden een aantal nieuwe belangen gemeld. Om de onafhankelijkheid van de richtlijn te

		Cholangiocarcinoma ENSCCA, onbetaald Advisory boards: Astra Zenca, Servier, BMS, Merck, Lilly, betaald aan mijn afdeling	cis vs pemigatinib (lokale PI) * KWF - PUMP-2: irresectabel intrahepatisch cholangiocarcinoom, fase 2 haalbaarheid intrahepatische chemotherapie gecombineerd met systemische chemotherapie (lokale PI) * KWF - ACTICCA: adjuvant, fase 3 gerandomiseerd gem cis vs capecitabine (lokale PI)	waarborgen zijn de betreffende modules meegelezen door twee onafhankelijke deskundigen vanuit de NIV.
Willemsen	Abdominaal radioloog Erasmus MC te Rotterdam	Geen	Geen	Geen restricties
Van Delden	Interventieradioloog, Amsterdam UMC	Geen	Geen	Geen restricties
Van Driel	MDL-arts, staflid, Erasmus MC Rotterdam - fulltime aanstelling	Geen	Geen	Geen restricties
Verheij	Klinisch patholoog (1 fte) met specialisme Hepato-pancreatobiliaire pathologie Amsterdam UMC	* Lid medisch Advies Raad Nederlandse Leverpatiënten Vereniging (NLV) (onbetaald) * Voorziter sectie HPB, Expertise Groep Gastrointestinale Pathologie, NVVP (onbetaald)	Geen	Geen restricties
Van der Post	Klinisch patholoog, Radboud Universitair medisch centrum	* Commissie lid Wetenschap NVVP (onbetaald) * Programmacommissie lid Kwaliteitsprojecten SKMS (vacatiegelden) * Voorzitter expertisegroep gastrointestinale pathologen EGIP, onderdeel NVVP (onbetaald)	<u>Extern gefinancierd onderzoek</u> * Stichting ADP - From bench to bedside, the molecular characteristics of galbladder cancer - Projectleider * KWF kankerbestrijding - Dissecting the role of aberrant E-cadherin signaling in the initiation and progression of diffuse-type gastric cancer - Projectleider * Stichting Hanarth Fonds - Unmasking the invisible cancer: digital detection of diffuse-type gastric	Geen restricties

			carcinomas - Projectleider	
Pek	Verpleegkundig specialist Erasmus MC Rotterdam. Pancreas- en galwegchircurgie specialist obstructie icterus	Geen	Geen	Geen restricties
Schrieks	Projectleider Patiëntenplatform Zeldzame Kanker	Geen	Geen	Geen restricties
Bode	* Patiënt vertegenwoordiger * Kinderfysiotherapeut MSc in ruste Zorggroep Almere (niet meer werkzaam) * Vrijwilliger bij patiëntenplatform Zeldzame kankers	Geen	Geen	Geen restricties
Weenink	Patiënt vertegenwoordiger Huisarts bij HAP Binnenstad Utrecht	Geen	Geen	Geen restricties

Inbreng patiëntenperspectief
Er werd aandacht besteed aan het patiëntenperspectief door het uitnodigen van het Patiëntenplatform Zeldzame Kankers om deel te nemen in de werkgroep en aan de schriftelijke knelpuntenanalyse. De verkregen input is meegenomen bij het opstellen van de uitgangsvragen, de keuze voor de uitkomstmaten en bij het opstellen van de overwegingen. De conceptrichtlijn zal tevens voor commentaar worden voorgelegd aan Patiëntenplatform Zeldzame Kankers.

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

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

Module	Uitkomst raming	Toelichting
Module 'Cross-sectionele beeldvorming'	Geen substantiële financiële gevolgen	Uit de toetsing volgt dat de aanbevelingen niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zullen hebben voor de collectieve uitgaven.
Module 'Locoregionale behandeling met TACE of SIRT voor iCCA'	Geen substantiële financiële gevolgen	Uit de toetsing volgt dat de aanbevelingen niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële

		financiële gevolgen zullen hebben voor de collectieve uitgaven.
Module 'Preoperatieve vena porta embolisatie'	Geen substantiële financiële gevolgen	Uit de toetsing volgt dat de aanbevelingen niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zullen hebben voor de collectieve uitgaven.
Module 'Indicatie resectie'	Geen substantiële financiële gevolgen	Uit de toetsing volgt dat de aanbevelingen niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zullen hebben voor de collectieve uitgaven.
Module 'Adjuvante systemische behandeling'	Geen substantiële financiële gevolgen	Uit de toetsing volgt dat de aanbevelingen niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zullen hebben voor de collectieve uitgaven.
Module 'Palliatieve systemische behandeling in de 1e lijn'	Geen substantiële financiële gevolgen	Uit de toetsing volgt dat de aanbevelingen niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zullen hebben voor de collectieve uitgaven.
Module 'Palliatieve systemische behandeling na de 1e lijn'	Geen substantiële financiële gevolgen	Uit de toetsing volgt dat de aanbevelingen niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zullen hebben voor de collectieve uitgaven.

Werkwijze

AGREE

Deze richtlijnmodule is opgesteld conform de eisen vermeld in het rapport Medisch Specialistische Richtlijnen 2.0 van de adviescommissie Richtlijnen van de Raad Kwaliteit. Dit rapport is gebaseerd op het AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers, 2010).

Knelpuntenanalyse en uitgangsvragen

Tijdens de voorbereidende fase inventariseerden de werkgroep de knelpunten in de zorg voor patiënten met een galweg- of galblaascarcinoom. De werkgroep beoordeelde de aanbeveling(en) uit de eerdere richtlijnmodules (NVvH, 2013) op noodzaak tot revisie. Tevens zijn er knelpunten aangedragen door de patiëntenvereniging en genodigde partijen tijdens de schriftelijke knelpuntenanalyse. De notulen van de tweede werkgroepvergadering waarin de resultaten van de schriftelijke knelpuntenanalyse zijn besproken zijn opgenomen als bijlage. Op basis van de uitkomsten van de knelpuntenanalyse zijn door de werkgroep concept-uitgangsvragen opgesteld en definitief vastgesteld.

Uitkomstmaten

Na het opstellen van de zoekvraag behorende bij de uitgangsvraag inventariseerde de werkgroep welke uitkomstmaten voor de patiënt relevant zijn, waarbij zowel naar gewenste als ongewenste effecten werd gekeken. Hierbij werd een maximum van acht uitkomstmaten gehanteerd. De werkgroep waardeerde deze uitkomstmaten volgens hun relatieve belang bij de besluitvorming rondom aanbevelingen, als cruciaal (kritiek voor de besluitvorming),

belangrijk (maar niet cruciaal) en onbelangrijk. Tevens definieerde de werkgroep tenminste voor de cruciale uitkomstmaten welke verschillen zij klinisch (patiënt) relevant vonden.

Methode literatuursamenvatting

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

Beoordelen van de kracht van het wetenschappelijke bewijs

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

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

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

Bij het beoordelen (graderen) van de kracht van het wetenschappelijk bewijs in richtlijnen volgens de GRADE-methodiek spelen grenzen voor klinische besluitvorming een belangrijke rol (Hultcrantz, 2017). Dit zijn de grenzen die bij overschrijding aanleiding zouden geven tot een aanpassing van de aanbeveling. Om de grenzen voor klinische besluitvorming te bepalen moeten alle relevante uitkomstmaten en overwegingen worden meegewogen. De grenzen

voor klinische besluitvorming zijn daarmee niet één op één vergelijkbaar met het minimaal klinisch relevant verschil (Minimal Clinically Important Difference, MCID). Met name in situaties waarin een interventie geen belangrijke nadelen heeft en de kosten relatief laag zijn, kan de grens voor klinische besluitvorming met betrekking tot de effectiviteit van de interventie bij een lagere waarde (dichter bij het nuleffect) liggen dan de MCID (Hultcrantz, 2017).

Overwegingen (van bewijs naar aanbeveling)

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

Formuleren van aanbevelingen

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

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

Implicaties van sterke en zwakke aanbevelingen voor verschillende richtlijngebruikers		
	Sterke aanbeveling	*Zwakke (conditionele) aanbeveling*
Voor patiënten	De meeste patiënten zouden de aanbevolen interventie of aanpak kiezen en slechts een klein aantal niet.	Een aanzienlijk deel van de patiënten zouden de aanbevolen interventie of aanpak kiezen, maar veel patiënten ook niet.
Voor behandelaars	De meeste patiënten zouden de aanbevolen interventie of aanpak moeten ontvangen.	Er zijn meerdere geschikte interventies of aanpakken. De patiënt moet worden ondersteund bij de keuze voor de interventie of

		aanpak die het beste aansluit bij zijn of haar waarden en voorkeuren.
Voor beleidsmakers	De aanbevolen interventie of aanpak kan worden gezien als standaardbeleid.	Beleidsbepaling vereist uitvoerige discussie met betrokkenheid van veel stakeholders. Er is een grotere kans op lokale beleidsverschillen.

Organisatie van zorg

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

Commentaar- en autorisatiefase

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

Literatuur

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Module 6 Cross-sectionele beeldvorming

Uitgangsvraag
Wat is de waarde van Magnetic Resonance Imaging (MRI) in de work-up van patiënten met een verdenking op kanker van de galweg of galblaas?

Inleiding
De meeste patiënten die zich presenteren met (een verdenking op) kanker van de galweg of galblaas ondergaan (na een abdominale echografie) een CT als eerste cross-sectionele diagnostiek. Vaak is het bij presentatie nog niet zeker of er sprake is van kanker. Patiënten met aspecifieke buikklachten krijgen dan een CT-abdomen met een veneuze contrast fase; patiënten met stille icterus krijgen een meerfasen CT-abdomen met zowel een blanco, arteriële als portoveneuze (en soms late) contrast fase. Een MRI is mogelijk van toegevoegde waarde. Allereerst is de MRI mogelijk beter in het onderscheid tussen benigne en maligne afwijkingen in de lever of galwegen, of voor het onderscheid tussen hepatocellulair carcinoom (HCC) en intrahepatisch cholangiocarcinoom (iCCA). Bovendien is de MRI mogelijk sensitiever voor metastasen in de lever. De detectie van metastasen bij galblaaskanker (GBC) en bij iCCA kan doorslaggevend zijn om af te zien van een chirurgische resectie. Tenslotte brengt een MRI voor patiënten met perihilair cholangiocarcinoom (pCCA) de galwegen mogelijk beter in beeld. Dit kan het interpreteren van de uitgebreid van de tumor en anatomische varianten van de galwegen vereenvoudigen. Hierdoor kan besloten worden tot een ander type lever resectie of om zelfs af te zien van een chirurgische resectie.

Search and select
A systematic review of the literature was performed to answer the following question:
What is the diagnostic accuracy, the cost-effectiveness, and the effect on survival of an additional MRI scan and what is the impact on the management of patients with (suspected) gallbladder or cholangiocarcinoma when an MRI is added to the diagnostic work-up?

P:	Patients suspected of cholangiocarcinoma (intrahepatic, perihilar, distal), and/or gall bladder carcinomas
I:	MRI
C:	-
R:	Pathology proven malignancy or a clinical course with a long enough follow-up
O:	Change of management, survival, cost-effectiveness, sensitivity, specificity

<u>Relevant outcome measures</u>
The guideline development group considered change in management and survival as a critical outcome measure and cost-effectiveness, sensitivity, and specificity as an important outcome measure for decision making.

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

The working group defined 10 MRI-scans to prevent 1 surgical exploration as a minimal clinically important difference.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched for systematic reviews with relevant search terms until 31-08-2021. Medline (via OVID) and Embase (via Embase.com) were also searched until 12-01-2021 for trials with relevant search terms. The detailed search strategy is depicted under the tab Methods. The systematic literature searches resulted in 1861 hits.

A preselection of potentially relevant literature for sections of the guideline was made by the guideline methodologists supporting the working group, excluding all obvious non-relevant articles for this section. When in slightest doubt the literature remained in the preselection. This resulted in the preselection of 238 hits from the total of 1861 hits. Thereafter, 11 studies were initially selected based on title and abstract screening by members of the working group. Studies were eligible for inclusion based on the following criteria: studies included patients suspected of cholangiocarcinoma's (intrahepatic, perihilar, distal) and/or gall bladder carcinomas and/or occult liver metastases all without evidence on an abdominal CT-scan, used MRI as an index test, used pathology or a clinical course with a long enough follow-up as reference tests, or assessed survival in a comparative study design (comparing to a strategy without MRI) or assessed cost-effectiveness (preferably in a Dutch setting) or assessed the accuracy or change in management of MRI (preferably as an add-on after a CT-scan). Studies reporting the diagnostic test accuracy of imaging modalities had to be systematic reviews. After reading the full text, seven studies were excluded (see the table with reasons for exclusion under the tab Methods), and four studies were included.

Results
Four systematic reviews were included in the analysis of the literature. Individual study characteristics and their risk of bias assessments are found in the published systematic reviews, respectively (Ruys, 2012; Zhang, 2015; You, 2018; You, 2019). Quality of the systematic reviews were appraised and summarized.

Summary of literature
Description of studies
Gallbladder cancer (GBC)
You (2018) performed a systematic review for the accuracy of DWI-MRI to differentiate benign and malignant gallbladder lesions. EMBASE and PubMed were searched up to the 15th of January 2017. Studies were selected when the sample both contained patients with benign or malignant gallbladder lesions, DWI-MRI was used as the index test, surgical findings or clinical follow-up was used as the reference test, a 2-by-2 table could be constructed, and study reports were original articles. Studies were excluded when they were performed in nonhumans, were case-reports or series, were reviews, guidelines, consensus statements, letters, editorials, clinical trials, conference abstracts, were not in the field of interest, had insufficient data to construct a 2-by-2 table, or had overlapping patient populations. Eight retrospective studies with consecutive recruitment were included. These included studies originated from Japan (n=4), South Korea (n=3), or Turkey (n=1). Two studies used follow-up as a reference standard, while the other six studies used histopathology. Two authors independently extracted characteristics and assessed the individual study quality using the QUADAS-2 tool. The authors judged the 'flow and timing' item (50% low risk, 50% unclear risk), the 'reference standard' item (100% low risk), the 'index test' item (75% low risk, 25% unclear risk), and the 'patient selection' item (63% low risk, 37% high risk) in the QUADAS-2 tool. Scanners in the studies used 1.5 or 3T and (single-shot) echo planar imaging in the axial plane. Minimum slice thickness ranged from 4 to 8 millimeters. Apparent diffusion coefficients ranged from 0.86 to 2.36 (not reported in one

study). The mean age of patients in the samples of included studies ranged from 56.2 years to 69 years, with a prevalence of GBC ranging between 14.3% to 56.6%.

Perihilar cholangiocarcinoma (pCCA)
Ruys (2012) performed a systematic review to assess the performance of MRI (among other techniques) in assessing the resectability in patient with pCCA. The databases MEDLINE (from January 1966), EMBASE (from January 1980), and CDSR were searched up to March 2011. Studies were included when at least 10 patients were included with pCCA, concerned the primary staging, the reference standard was surgical of pathological confirmation, providing sufficient data for portal vein involvement, hepatic artery involvement, lymph node involvement, presence of distant metastasis, ductal extent. Studies were excluded when data from patients with pCCA could not be obtained or when duplicate data was reported (only the most recent study was included). Reference lists of included studies were manually searched for additional studies. Studies were assessed with the QUADAS-tool. Three of the included studies retrospectively assessed the performance of MRI (n=3 ductal extent, n=1 portal vein involvement). None of the included studies used MRI to assess the hepatic artery involvement, lymph node involvement, or metastases.

Zhang (2015) performed a systematic review and meta-analysis to assess the resectability with imaging modalities in patients with pCCA. The MEDLINE, EMBASE, CancerLit, and Cochrane Library databases were searched from January 1980 to March 2015. Studies were selected when imaging (CT, MRI, PET/CT) was used to evaluate the resectability, two-by-two tables could be constructed per-patient, 10 or more patients were included, and when published in English. The most recent or detailed articles were included when multiple articles presented the same data. A total of 16 studies were included, of which 5 studies concerned assessment with MRI (one study overlapped with Ruys, 2012) in 256 patients. Mean age within the study samples ranged from 53 to 66 years. The authors used the QUADAS-tool to appraise the risk of bias of the included studies. All included studies for MRI scored 12 points on the QUADAS tool.

Intrahepatic cholangiocarcinoma (iCCA)
You (2019) performed a systematic review for the accuracy of imaging features of contrast-enhanced MRI to differentiate between a hepatocellular carcinoma (HCC) and iCCA. EMBASE and PubMed were searched up to the 31st of July 2018. Studies were selected when they were original studies with a sample of patients with HCC and iCCA, when patients underwent a contrast-enhanced MRI, where patients had a histopathological diagnosis of HCC or iCCA, when the study design was observational, and when 2-by-2 tables could be constructed. Studies were excluded when they were case reports or series, reviews, editorials, letters, comments, conference proceedings, when not in the field of interest, when the 2-by-2 table could not be constructed, and when there were overlapping study populations. Fourteen studies were included. One author extracted the data and was checked by a second author. Two authors assessed the individual study quality using the QUADAS-2 tool. Authors judged the ‘flow and timing’ (10 studies at unclear risk, 4 studies at low risk), ‘index test’ (all studies at low risk), ‘reference standard’ (all studies at low risk), and ‘patient selection’ (3 studies at high risk, 11 studies at low risk). MR imaging was acquired in the studies using 1.5 to 3.0T with gadoxetic acid, gadopentetate dimeglumine (with/without ferucarbotran), gadoderate meglumine, gadovist, and/or gadodiamide as contrast agents. Minimum slice thickness ranged from 2 to 5 millimeters (not reported in one study) while various sequences were used (e.g., T1W1, T2WI, T1DCE, IP-OP, DWI, T1CE). The mean age of the samples from the includes studies ranged from 46 to 70 years in patients with HCC and from 55 to 68.3 years for patients with an iCCA. Six of the included studies recruited patients with chronic liver

disease only. The other eight studies recruited a more heterogeneous patient population consisting of patients with normal livers and patients with chronic liver disease.

Results

Gallbladder carcinoma

Change of management

No study could be included that reported the proportion of changes in management when using a diagnostic strategy with MRI for patients suspected of GBC.

Survival

No study could be included that reported on the effects of using a diagnostic strategy with MRI on the survival of patients suspected of GBC.

Cost-effectiveness

No study could be included that reported the cost-effectiveness of using a diagnostic strategy with MRI for patients suspected of GBC.

Sensitivity

You (2018) reported the overall sensitivity of DWI-MRI to differentiate benign from malignant gallbladder lesions, pooling data from eight studies. A sensitivity of 0.91 (95%CI: 0.91-0.91) was reported (I^2: 56%). When reporting the sensitivity of the qualitative assessment of DWI (i.e. visual assessment), You (2018) found a sensitivity of 0.90 (95%CI: 0.77-0.96, I^2: 71%) by pooling data from six studies. Pooled sensitivity of quantitative DWI assessment was 0.82 (95%CI: 0.73-0.89, I^2: 38%) from six studies.

Specificity

You (2018) reported the overall specificity of DWI-MRI to differentiate malign from benign gallbladder lesions, pooling data from eight studies (I^2: 80%). The reported specificity was 0.87 (95%CI: 0.87-0.87) was reported. The pooled specificity of the qualitative assessment of DWI (i.e. visual assessment) was 0.87 (95%CI: 0.78-0.92, I^2: 77%) from six studies. Quantitative assessment of DWI showed a specificity of 0.86 (95%CI: 0.68-0.94, I^2: 84%) pooling data from six studies.

Perihilar cholangiocarcinoma

Change of management

No study could be included that reported the proportion of changes in management when using a diagnostic strategy with MRI for patients suspected of pCCA.

Survival

No study could be included that reported on the effects of using a diagnostic strategy with MRI on the survival of patients suspected of pCCA.

Cost-effectiveness

No study could be included that reported the cost-effectiveness of using a diagnostic strategy with MRI for patients suspected of pCCA.

Sensitivity

Ruys (2012) reported that one study used MRI to assess the portal vein involvement. The sensitivity was 0.79 (95%CI: 0.49-0.95). Zhang (2015) used a fixed effects model to pool 5

studies (I^2: 48%) and reported a pooled sensitivity estimate of 0.94 (95%CI: 0.90-0.97, fixed effects model) for resectability assessment.

Specificity
Ruys (2012) reported that one study used MRI to assess the portal vein involvement. The specificity was 0.00 (95%CI: 0.00-0.71), although only 1 patient without the target condition was assessed. Zhang (2015) reported a pooled specificity estimate of 0.71 (95%CI: 0.60-0.81) from 5 studies (fixed effects, I^2: 0%) for resectability assessment with MRI.

Accuracy
Three studies included in Ruys (20212) assessed the ductal extend with MRI. Accuracy was calculated as the correct diagnosis of the ductal extent following the Bismuth-Corlette classification divided by the total number of patients. The calculated accuracies from three studies were: 0.80 (12/15), 0.75 (15/20), and 0.71 (10/14), respectively.

Intrahepatic cholangiocarcinoma
Change of management
No study could be included that reported the proportion of changes in management when using a diagnostic strategy with MRI for patients suspected of iCCA.

Survival
No study could be included that reported on the effects of using a diagnostic strategy with MRI on the survival of patients suspected of iCCA.

Cost-effectiveness
No study could be included that reported the cost-effectiveness of using a diagnostic strategy with MRI for patients suspected of iCCA.

Sensitivity
You (2019) pooled the sensitivity of eight contrast-enhanced MRI features individually that favour iCCA in differentiating with HCC. Sensitivities of single MRI features are reported in Table 1.

Specificity
You (2019) pooled the specificity of eight contrast-enhanced MRI features individually that favour iCCA in differentiating with HCC. Specificities of single MRI features are reported in Table 1.

Table 1 – Sensitivity and specificity of MRI features favouring iCCA in differentiating with HHC (from You, 2019).

MRI feature	Sensitivity (95%CI)	Specificity (95%CI)
Lobulate shape	0.55 (95%CI: 0.39-0.70)	0.82 (95%CI: 0.60-0.93)
Capsular retraction	0.26 (95%CI: 0.19-0.34)	0.95 (95%CI: 0.88-0.98)
Arterial rim enhancement	0.66 (95%CI: 0.44-0.80)	0.93 (95%CI: 0.72-0.99)
Progressive enhancement	0.48 (95%CI: 0.24-0.73)	0.96 (95%CI: 0.91-0.99)
Persistent enhancement	0.24 (95%CI: 0.11-0.44)	0.98 (95%CI: 0.90-1.00)

Target appearance on diffusion-weighted images	0.62 (95%CI: 0.41-0.83)	0.91 (95%CI: 0.53-0.99)
Target appearance on hepatobiliary phase images	0.65 (95%CI: 0.41-0.83)	0.87 (95%CI: 0.44-0.98)
Bile duct dilatation	0.40 (95%CI: 0.29-0.51)	0.95 (95%CI: 0.92-0.97)

Level of evidence of the literature

Gallbladder carcinoma

The level of evidence regarding the outcome measure sensitivity and specificity were downgraded by 3 levels because of study limitations (1 level for risk of bias: authors [You, 2018] indicated that three studies had a high risk for patient selection [two studies excluded wall thickening <3 or 4mm, the other excluded patients with obvious inflammations); conflicting results (1 level for inconsistency: unexplained heterogeneity); applicability (1 level due to indirectness: authors [You, 2018] indicated that there were high concerns due to different cut-off values used to differentiate between benign and malign in quantitative assessment); publication bias was assessed by the authors of the systematic review [You, 2018] with the Deek's funnel plot and the asymmetry test, and concluded that there was no influence of publication bias. Imprecision was not downgraded, because inconsistency was already downgraded which potentially caused a wide confidence interval in the summary estimates.

The level of evidence regarding the outcome measures change in management, survival, and cost-effectiveness could not be graded since none of the included studies reported data for these outcomes.

Perihilar cholangiocarcinoma

The level of evidence regarding the outcome measure change of management, survival, and cost-effectiveness could not be graded since none of the included studies reported data for these outcomes.

The level of evidence regarding the outcome measure sensitivity was downgraded by 1 levels because of study limitations (not downgraded for risk of bias: Zhang 2015 assigned 12 out of 14 points to each of the included studies for MRI [although not specified on which items]); number of included patients (1 level for imprecision: only n=179 and n=15 were used for sensitivity).

The level of evidence regarding the outcome measure specificity was downgraded by 2 levels because of conflicting results (inconsistency: although results between systematic reviews are different we did not downgrade because Ruys 2012 only used 1 study that had n=1 assessed for specificity); and number of included patients (2 level for imprecision: Wide confidence interval of the pooled estimate, and n=78 and n=1 were used for specificity).

Intrahepatic cholangiocarcinoma

The level of evidence regarding the outcome measures change in management, survival, and cost-effectiveness could not be graded since none of the included studies reported data for these outcomes.

The level of evidence regarding the outcome measure sensitivity and specificity were downgraded by 3 levels because of study limitations (1 level for risk of bias: 10 out of 14 studies did not report the time between index test and reference test); conflicting results (2 levels for inconsistency: statistical measure for heterogeneity (I^2) is not readable from the figures, eyeballing the forest plots of the relevant MRI features the plots show large unexplained heterogeneity); publication bias could not be assessed in diagnostic test accuracy studies. Imprecision was not downgraded, because inconsistency was already downgraded which potentially caused a wide confidence interval in the summary estimates of the imaging features.

Conclusions

Gallbladder carcinoma

NO GRADE	No study could be included that reported data on the effects of using a diagnostic strategy with MRI on the survival of patients suspected of a GBC.

NO GRADE	No study could be included that reported data on the change in management when using a diagnostic strategy with MRI for patients suspected of a GBC.

NO GRADE	No study could be included that reported data on the cost-effectiveness of using a diagnostic strategy with MRI in patients suspected of a GBC.

VERY LOW GRADE	The confidence in the sensitivity of DWI-MRI found in literature to differentiate GBC from a benign lesion in patients suspected of a GBC is very low. *Sources: You, 2018*

VERY LOW GRADE	The confidence in the specificity of DWI-MRI found in literature to differentiate a malign GBC from a benign lesion in patients suspected of a GBC is very low. *Sources: You, 2018*

Perihilar cholangiocarcinoma

NO GRADE	No study could be included that reported data on the effects of using a diagnostic strategy with MRI on survival of patients suspected of a pCCA.

NO GRADE	No study could be included that reported data on the change in management when using a diagnostic strategy with MRI for patients suspected of a pCCA.

NO GRADE	No study could be included that reported data on the cost-effectiveness of using a diagnostic strategy with MRI in patients suspected of a pCCA.

MODERATE GRADE	The confidence in the sensitivity of MRI found in literature to assess the resectability of a perihilar cholangiocarcinoma in patients with a pCCA is moderate. *Sources: Ruys, 2012; Zhang, 2015*

LOW GRADE	The confidence in the specificity of MRI found in literature to assess the resectability of a pCCA in patients with a pCCA is low. *Sources: Ruys, 2012; Zhang, 2015*

Intrahepatic cholangiocarcinoma

NO GRADE	No study could be included that reported data on the effects of using a diagnostic strategy with MRI on survival of patients suspected of an iCCA.

NO GRADE	No study could be included that reported data on the change in management when using a diagnostic strategy with MRI for patients suspected of an iCCA.

NO GRADE	No study could be included that reported data on the cost-effectiveness of using a diagnostic strategy with MRI in patients suspected of an iCCA.

VERY LOW GRADE	The confidence in the sensitivity of DWI-MRI found in the literature to differentiate an iCCA from a HCC in patients suspected of an iCCA is very low. *Sources: You, 2019*

VERY LOW GRADE	The confidence in the sensitivity of DWI-MRI found in literature to differentiate an iCCA from a HCC in patients suspected of an iCCA is very low. *Sources: You, 2019*

Overwegingen – van bewijs naar aanbeveling

De zoekstrategie heeft geen studies opgeleverd die data rapporteerden over de effecten van MRI op de overleving van patiënten met een galweg- of galblaascarcinoom. Tevens werd er geen enkele studie gevonden die rapporteerde over de verandering van het beleid door een aanvullende MRI of de kosteneffectiviteit hiervan. Alleen voor de diagnostische accuratesse van MRI waren studies beschikbaar. Echter, het vertrouwen in de gepoolde test karakteristieken werd overwegend als laag beoordeeld.

<u>Galblaascarcinoom (GBC): onderscheid benigne en (pre)maligne afwijking</u>

Solide afwijkingen van de galblaas worden meestal initieel gevonden met een conventionele echo abdomen. Veelvoorkomende benigne afwijkingen zijn poliepen, cholecystotlithiasis, en adenomyomatosis. MRI (met DWI) bleek redelijk goed in het differentiëren tussen galblaaskanker en benigne galblaas afwijkingen met een gepoolde sensitiviteit van 0,90 en specificiteit van 0,87. Dit wordt onderschreven in een ander systematisch literatuuronderzoek (sensitiviteit van 0,87; specificiteit van 0,84), die niet in de huidige

zoekstrategie gevonden was (Kuipers 2021). Alternatieve diagnostiek is een echo met contrast of een CT om te beoordelen of de afwijking contrast opneemt. Solide afwijkingen die contrast opnemen zijn verdacht voor GBC of een premaligne galblaaspoliep (zie module 'indicatie resectie'. Er is onvoldoende bewijs om te concluderen of MRI beter is dan CT of echo met contrast om dit onderscheid te maken. Een target echo met aandacht voor andere aspecten dan de grootte van de poliep draagt bij aan verdere differentiatie. Een lobulair oppervlak, sessiele poliep, verdikking van de focale wand, vasculaire kern en hypoechogeen intern patroon of foci zijn geassocieerd met neoplastische poliepen en zouden aanvullende argumenten opleveren zijn voor een cholecystectomie. Hyperechoïsch intern patroon of foci komen vaker voor bij cholesterolpoliepen.

Perihiliair cholangiocarcinoom (pCCA): resectabiliteit

Resectabiliteit van pCCA (zie ook Module 'indicatie resectie') hangt af van de betrokkenheid van de vena portae en de arteria hepatica, evenals de uitgebreidheid van de tumor in de galwegen (Bismuth classificatie). De kans is 30%-50% dat tijdens de operatie blijkt dat pCCA toch niet resectabel is. Dit komt door occulte metastasen op het peritoneum of de lever of door lokale uitgebreidheid, die door preoperatieve beeldvorming is onderschat. Een MRI beoogt de kans op een operatie zonder resectie te verkleinen door detectie van occulte lever metastasen en betere beoordeling van de uitgebreidheid van de tumor in de galwegen. MRI bleek enigszins in staat om de resectabiliteit van pCCA te beoordelen met een gepoolde sensitiviteit van 0,94 en specificiteit van 0,71. Hoewel de test karakteristieken redelijk zijn, is niet onderzocht hoe vaak de MRI heeft geleid tot een verandering in beleid of een verbetering in overleving.

Intrahepatisch cholangiocarcinoom (iCCA): onderscheid met HCC

Het onderscheid tussen iCCA en een hepatocellulair carcinoom (HCC) is vooral bij onderliggende lever ziekte en kleine tumoren soms niet eenduidig. Verschillende aspecten van de MRI (met contrast) zijn onderzocht voor de differentiatie tussen HCC en iCCA. De gepoolde specificiteit van kapsel intrekking, randaankleuring en progressieve/persisterende aankleuring was groter dan 93%. De gepoolde sensitiviteit was echter kleiner dan 66%. Vooral de specificiteit is goed, maar de meerwaarde ten opzichte van CT is onvoldoende onderzocht.

Detectie levermetastasen

De aanwezigheid van levermetastasen is (vrijwel) altijd doorslaggevend om geen chirurgische resectie te doen voor galweg- en galblaaskanker. De kans om bij diagnostische laparoscopie occulte lever of peritoneale metastasen te vinden varieert in studies van 10% tot 30%. MRI is niet sensitief voor peritoneale metastasen, maar mogelijk sensitiever voor de detectie van levermetastasen dan CT. Helaas zijn er geen studies gevonden die MRI en CT vergelijken ten aanzien van de detectie van levermetastasen. Een prospectieve studie (CAMINO trial) heeft recent de aanvullende waarde van MRI onderzocht voor patiënten met colorectale levermetastasen. MRI ontdekte bij 31% van de patiënten extra metastasen resulterend in een verandering van beleid (publicatie volgt). Het is aannemelijk dat MRI ook voor galweg- en galblaaskanker meerwaarde heeft voor de detectie van lever metastasen die occult zijn op CT. Bij pCCA en dCCA komen lever metastasen weinig voor bij initiële presentatie. Bij iCCA en GBC is de kans hierop groter en dus ook de kans dat het beleid verandert door MRI.

Detectie lymfkliermetastasen

Hoewel de lymfeklierstatus relevant is voor stadiëring van galweg- en galblaaskanker, is het onduidelijk wat de optimale beeldvorming is voor de detectie van lymfekliermetastasen (de

Savornin Lohman, 2019). Studies over CT en MRI laten veel heterogeniteit zien in zowel de sensitiviteit als specificiteit, en zowel CT als MRI lijken op dit moment nog onbetrouwbaar te zijn voor de detectie van lymfekliermetastasen kleiner dan 10 millimeter (de Savornin Lohman, 2019). MRI heeft geen toegevoegde waarde voor de detectie van lymfklieren. Endoscopische echografie met lymfklierbiopten zou hier van meerwaarde kunnen zijn, maar is nog niet prospectief onderzocht.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Voor patiënten is het grootste nadeel dat het gemiddeld een dagdeel kost om naar het ziekenhuis te gaan voor een MRI. De kans op complicaties (b.v., contrastallergie) is gering. Sommige patiënten willen geen MRI ondergaan in verband met claustrofobie. Tenslotte is er nog een kleine kans dat de MRI fout-positieve bevindingen heeft waardoor een patiënt aanvullende diagnostiek nodig heeft (zoals een leverbiopt) of ten onrechte geen chirurgische exploratie ondergaat.

Kosten (middelenbeslag)
De kosten van de MRI zelf zijn ongeveer 250 euro. Dit kan kosteneffectief zijn als bij een aanzienlijk percentage (b.v., 10%) dankzij de bevindingen van de MRI een verandering in beleid optreedt, zoals het niet verrichten van een diagnostische laparoscopie of soms zelfs grote leverresectie.

Aanvaardbaarheid, haalbaarheid en implementatie
Het inzetten van MRI voor alle patiënten met iCCA, pCCA of GBC die in aanmerking komen voor een resectie op basis van CT, zou haalbaar zijn omdat het om slechts ongeveer 150 patiënten per jaar gaat. De aanbevelingen om een MRI te overwegen zijn in overeenstemming met de huidige zorg in de praktijk.

Aanbevelingen
Aanbeveling-1
Het onderscheid tussen een benigne en (pre)maligne afwijking van de galblaas is soms moeilijk te maken op basis van een CT.

Overweeg een MRI of echo met contrast voor patiënten met een galblaas afwijking als er op CT onvoldoende zekerheid is of er sprake is van een benigne of een (pre)maligne afwijking.

Aanbeveling-2
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Er is onvoldoende bewijs om MRI als standaard aanvullende diagnostiek te adviseren voor de diagnose van intrahepatisch cholangiocarcinoom.

Overweeg een MRI voor de differentiatie met andere maligne leverlaesies (met name hepatocellulair carcinomen) bij patiënten met een verdenking op een intrahepatisch cholangiocarcinoom als dit het beleid kan wijzigen. Zie hiervoor ook de module diagnostiek in de richtlijn ‘Hepatocellulair carcinoom’.

Aanbeveling-3

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Er is onvoldoende bewijs om MRI als standaard aanvullende diagnostiek te adviseren voorafgaand aan chirurgische exploratie. Echter, een MRI kan aanvullende informatie verschaffen naast een CT als er onzekerheid is over de uitgebreidheid van de tumor in de galwegen bij patiënten met pCCA die in aanmerking komen voor een chirurgische exploratie.

Overweeg een MRI als er op CT onzekerheid bestaat bij patiënten met een mogelijk resectabel perihiliair cholangiocarcinoom over de uitbreiding van de tumor in de galwegen (Bismuth-Corlette classificatie) en dit het beleid kan wijzigen.

Aanbeveling-4
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Patiënten met iCCA en GBC hebben bij presentatie soms kleine intrahepatische metastasen ontwikkelen, die niet goed zichtbaar zijn met CT. Een MRI heeft mogelijk meerwaarde voor de detectie van deze occulte metastasen.

Overweeg een MRI bij patiënten met intrahepatisch cholangiocarcinoom en galblaascarcinoom, die in aanmerking komen voor een resectie voor de detectie van occulte levermetastasen.

Literatuur

Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010 Jun;17(6):1471-4. doi: 10.1245/s10434-010-0985-4. PMID: 20180029.

Kuipers H, Hoogwater FJ, Holtman GA, van der Hoorn A, de Boer MT, de Haas RJ. Clinical value of diffusion-weighted MRI for differentiation between benign and malignant gallbladder disease: a systematic review and meta-analysis. Acta Radiol. 2021 Aug;62(8):987-996. doi: 10.1177/0284185120950115. Epub 2020 Aug 23. PMID: 32830511.

Ruys AT, van Beem BE, Engelbrecht MR, Bipat S, Stoker J, Van Gulik TM. Radiological staging in patients with hilar cholangiocarcinoma: a systematic review and meta-analysis. Br J Radiol. 2012 Sep;85(1017):1255-62. doi: 10.1259/bjr/88405305. PMID: 22919007; PMCID: PMC3487057.

de Savornin Lohman EAJ, de Bitter TJJ, van Laarhoven CJHM, Hermans JJ, de Haas RJ, de Reuver PR. The diagnostic accuracy of CT and MRI for the detection of lymph node metastases in gallbladder cancer: A systematic review and meta-analysis. Eur J Radiol. 2019 Jan;110:156-162. doi: 10.1016/j.ejrad.2018.11.034. Epub 2018 Nov 28. PMID: 30599854.

You MW, Yun SJ. Diagnostic performance of diffusion-weighted imaging for differentiating benign and malignant gallbladder lesions: A systematic review and meta-analysis. J Magn Reson Imaging. 2018 Nov;48(5):1375-1388. doi: 10.1002/jmri.26035. Epub 2018 Apr 20. PMID: 29676860.

You MW, Yun SJ. Differentiating between hepatocellular carcinoma and intrahepatic cholangiocarcinoma using contrast-enhanced MRI features: a systematic review and meta-analysis. Clin Radiol. 2019 May;74(5):406.e9-406.e18. doi: 10.1016/j.crad.2018.12.016. Epub 2019 Jan 28. PMID: 30704667.

Zhang H, Zhu J, Ke F, Weng M, Wu X, Li M, Quan Z, Liu Y, Zhang Y, Gong W. Radiological Imaging for Assessing the Respectability of Hilar Cholangiocarcinoma: A Systematic

Review and Meta-Analysis. Biomed Res Int. 2015;2015:497942. doi: 10.1155/2015/497942. Epub 2015 Sep 1. PMID: 26448940; PMCID: PMC4569758.

Bijlagen bij module 6 Cross-sectionele beeldvorming

Table of quality assessment for systematic reviews of diagnostic studies

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

Research question:

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Assessment of scientific quality of included studies?[5] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[6] Yes/no/unclear	Potential risk of publication bias taken into account?[7] Yes/no/unclear	Potential conflicts of interest reported?[8] Yes/no/unclear
You 2018	Yes Reason: PICO elements could have been described more precisely to be more informative and specific. Explicit inclusion and exclusion criteria were given.	Yes Reason: search date, sources and strategy were described.	Yes Reason: Reasons were provided and excluded studies were referenced in the text	Yes Reason: characteristics of studies and patient samples were provided. Characteristics seem relevant.	Yes Reason: QUADAS-2 was used.	Unclear Reason: Magnet strength and slice thickness were significant factors in the meta-regression analysis.	Yes Reason: Deek's funnel plot and asymmetry test were used.	No Reason: not reported for the included studies.
You 2019	Yes Reason: PICO elements could have been described more precisely to be more informative and specific. Explicit inclusion and exclusion criteria were given.	Yes Reason: search date, sources and strategy were described.	Yes Reason: Reasons were provided and excluded studies were referenced in the text	Yes Reason: characteristics of studies and patient samples were provided. Characteristics seem relevant.	Yes Reason: QUADAS-2 was used.	Unclear Reason: meta-regression showed that the liver background was a significant factor for heterogeneity.	Unclear Reason: Reported in the methods but does not seem to be reported in the results or discussion.	No Reason: not reported for the included studies.
Ruys 2012	Yes Reason: PICO elements could have been described more precisely to be more informative and specific. Explicit inclusion and exclusion criteria were given.	Yes Reason: search date, sources and strategy were described	No Reason: Reasons were provided but excluded studies were not referenced.	Yes Reason: Provided in a table, but could be more elaborate.	Yes Reason: QUADAS-1 was used.	Unclear Reason: Meta-analysis was not performed for MRI	Yes Reason: discussed in the discussion section. Although no plots were constructed.	No Reason: not reported for the included studies.
Zhang 2015	Yes Reason: PICO elements could have been described more precisely to be more informative and specific. Explicit inclusion criteria were given.	Yes Reason: search date, sources and strategy were described	No Reason: Reasons were provided but excluded studies were not referenced.	Yes Reason: Provided in a table, but could be more elaborate.	Yes Reason: QUADAS-1 was used.	Unclear Reason: not enough information provided	Yes Reason: Deek's funnel plot was used	No Reason: not reported for the included studies.

1. Research question (PICO) and inclusion criteria should be appropriate (in relation to the research question to be answered in the clinical guideline) and predefined

2. Search period and strategy should be described; at least Medline searched
3. Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons
4. Characteristics of individual studies relevant to the research question (PICO) should be reported
5. Quality of individual studies should be assessed using a quality scoring tool or checklist (preferably QUADAS-2; COSMIN checklist for measuring instruments) and taken into account in the evidence synthesis
6. Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, diagnostic tests (strategy) to allow pooling? For pooled data: at least 5 studies available for pooling; assessment of statistical heterogeneity and, more importantly (see Note), assessment of the reasons for heterogeneity (if present)? Note: sensitivity and specificity depend on the situation in which the test is being used and the thresholds that have been set, and sensitivity and specificity are correlated; therefore, the use of heterogeneity statistics (p-values; I^2) is problematic, and rather than testing whether heterogeneity is present, heterogeneity should be assessed by eye-balling (degree of overlap of confidence intervals in Forest plot), and the reasons for heterogeneity should be examined.
7. There is no clear evidence for publication bias in diagnostic studies, and an ongoing discussion on which statistical method should be used. Tests to identify publication bias are likely to give false-positive results, among available tests, Deeks' test is most valid. Irrespective of the use of statistical methods, you may score "Yes" if the authors discuss the potential risk of publication bias.
8. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.

Evidence table for diagnostic test accuracy studies

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Yang 2017	Type of study[1]: Retrospective study on prospective collected data. Setting and country: Hospital, China Funding and conflicts of interest: authors declare they have no conflict of interest. Statements about funding do not seem to be reported.	Inclusion criteria: Major clinical manifestations of jaundice, rising CA19-9 level Exclusion criteria: Biliary obstruction from pancreatic mass, motion artifacts on imaging, incomplete data N=63 Prevalence: 39/63 (61.9%)	Describe index test: MRCP (2D/3D) + DWI MRI Cut-off point(s): MCRP: non-uniform dilatation of intrahepatic/extrahepatic duct + common bile duct with irregular narrow edge + asymmetric stenosis and abrubt cut-off MRI qualitative: high signal in DWI (b=0) with increasing signal between b=500-1200 compared to surrounding tissue + ADC-map has low signal intensity with a relative low ADC-value MRI quantitative: unclear Comparator test[2]: None Cut-off point(s):	Describe reference test[3]: Histology or cytology (not described). Cut-off point(s): Not described	Time between the index test en reference test: Unclear For how many participants were no complete outcome data available? None other than those excluded in the patient selection: 2 patients were excluded because they had incomplete data. Reasons for incomplete outcome data described? Not described	Outcome measures and effect size (include 95%CI and p-value if available)[4]: <u>Sensitivity</u> MCRP + DWI at b=500: sensitivity =0.79 (95%CI: 0.64-0.91). MRCP + DWI at both b=500 and b=1200: Sensitivity = 0.95 (95%CI: 0.83-0.99) <u>Specificity</u> MRCP + DWI at b=500: Specificity = 0.75 (95%CI: 0.53-0.90) MRCP + DWI at both b=500 and b=1200: Specificity = 1.00 (95%CI: 0.86-1.00)	

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

[2] Comparator test is vergelijkbaar met de C uit de PICO van een interventievraag. Er kunnen ook meerdere tests worden vergeleken. Voeg die toe als comparator test 2 etc. Let op: de comparator test kan <u>nooit</u> de referentiestandaard zijn.

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

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

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
		Mean age: 63 years Sex: 34 M / 29 F Other important characteristics: Extrahepatic cholangio carcinoma type: Hepatic hilum: 19 Common bile duct: 14 Ampullar region: 6	na				

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

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Yang 2017	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No. Reason: 33 patients were excluded from analyses due to a final diagnosis of pancreatic cancer which may initially have been suspected cholangiocarcinomas / motion artifacts on imaging should probably not be excluded but assessed and included in the analysis / two patients were excluded due to insufficient data	Were the index test results interpreted without knowledge of the results of the reference standard? Yes Reason: two observers were not involved in the acquisition, and were blinded to clinical information, surgical information, and histological information. If a threshold was used, was it pre-specified? Yes Reason: the use of signal intensity, signal variation and adc-value were described for qualitative assessment, however the exact thresholds could have been described more precisely (e.g. 'a relatively low adc'). For the qualitative assessment, the adc-value under several b-values was measured. However, a threshold did not seem to be described.	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes	Was there an appropriate interval between index test(s) and reference standard? Unclear Reason: does not seem to be stated in the methods or results. Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No Reason: diagnosed by histology or cytology Were all patients included in the analysis? Yes Reason: all 63 remaining patients seem to be included in the analyses.	Are there concerns that the included patients do not match the review question? Yes Reason: patients did not seem to receive a CT prior to the MRI, but rather the MRI was used as an add-on to MRCP. Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: HIGH** Reason: excluding certain cases might alter the discriminative	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: LOW**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: HIGH** Reason: two different reference standards were used. It is unclear	

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
	capabilities of the index test in the remaining sample, compared to its capabilities when these cases would not have been excluded.			how many cases received cytology and how many received histology. It is unclear what the time interval between index and reference test was.	

Judgments on risk of bias are dependent on the research question: some items are more likely to introduce bias than others, and may be given more weight in the final conclusion on the overall risk of bias per domain:

Patient selection:

- Consecutive or random sample has a low risk to introduce bias.
- A case control design is very likely to overestimate accuracy and thus introduce bias.
- Inappropriate exclusion is likely to introduce bias.

Index test:

- This item is similar to “blinding” in intervention studies. The potential for bias is related to the subjectivity of index test interpretation and the order of testing.
- Selecting the test threshold to optimise sensitivity and/or specificity may lead to overoptimistic estimates of test performance and introduce bias.

Reference standard:

- When the reference standard is not 100% sensitive and 100% specific, disagreements between the index test and reference standard may be incorrect, which increases the risk of bias.
- This item is similar to “blinding” in intervention studies. The potential for bias is related to the subjectivity of index test interpretation and the order of testing.

Flow and timing:

- If there is a delay or if treatment is started between index test and reference standard, misclassification may occur due to recovery or deterioration of the condition, which increases the risk of bias.
- If the results of the index test influence the decision on whether to perform the reference standard or which reference standard is used, estimated diagnostic accuracy may be biased.
- All patients who were recruited into the study should be included in the analysis, if not, the risk of bias is increased.

Judgement on applicability:

Patient selection: there may be concerns regarding applicability if patients included in the study differ from those targeted by the review question, in terms of severity of the target condition, demographic features, presence of differential diagnosis or co-morbidity, setting of the study and previous testing protocols.

Implementatieplan bij module 6 Cross-sectionele beeldvorming

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Aanbeveling 1 Overweeg een MRI of echo met contrast voor patiënten met een galblaas afwijking als er op CT onvoldoende zekerheid is of er sprake is van een benigne of een (pre)maligne afwijking.	< 1 jaar	Geen / kostenreductie	Bekendheid met richtlijn	Diagnose galblaas poliepen veelal in talrijke niet-academische ziekenhuizen,	Publicatie richtlijn	Wetenschappelijke verenigingen	
Aanbeveling 2 Overweeg een MRI voor de differentiatie met andere maligne leverlaesies (met name hepatocellulair carcinomen) bij patiënten met een verdenking op een intrahepatisch cholangiocarcinoom als dit het beleid kan wijzigen. Zie	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn	Wetenschappelijke verenigingen	

hiervoor ook de module diagnostiek in de richtlijn 'Hepatocellulair carcinoom'.							
<u>Aanbeveling 3</u> Overweeg een MRI als er op CT onzekerheid bestaat bij patiënten met een mogelijk resectabel perihiliair cholangiocarcinoom over de uitbreiding van de tumor in de galwegen (Bismuth-Corlette classificatie) en dit het beleid kan wijzigen.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn	Wetenschappelijke verenigingen	
<u>Aanbeveling 4</u> Overweeg een MRI bij patiënten met intrahepatisch cholangiocarcinoom en galblaascarcinoom, die in aanmerking komen voor een resectie voor de detectie van occulte levermetastasen.	< 1 jaa	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn	Wetenschappelijke verenigingen	

Table of excluded studies

Author and year	Reason for exclusion
Tamburrino, D. and Riviere, D. and Yaghoobi, M. and Davidson, B. R. and Gurusamy, K. S. (2016), Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer	seems to be the wrong population
Zhao, X. Y. and Zhou, S. and Wang, D. Z. and He, W. and Li, J. X. and Zhang, S. (2015), Differential Diagnosis of Malignant Biliary Tract Cancer from Benign Tissues using Apparent Diffusion Coefficient Measurements with Diffusion Weighted Imaging in Asians	did not seem to assess accuracy
Gardner, C. S. and Bashir, M. R. and Marin, D. and Nelson, R. C. and Choudhury, K. R. and Ho, L. M. (2015), Diagnostic performance of imaging criteria for distinguishing autoimmune cholangiopathy from primary sclerosing cholangitis and bile duct malignancy	seems to be wrong target conditions
Eaton, J. E. and Welle, C. L. and Bakhshi, Z. and Sheedy, S. P. and Idilman, I. S. and Gores, G. J. and Rosen, C. B. and Heimbach, J. K. and Taner, T. and Harnois, D. M. and Lindor, K. D. and LaRusso, N. F. and Gossard, A. A. and Lazaridis, K. N. and Venkatesh, S. K. (2020), Early cholangiocarcinoma detection with magnetic resonance imaging versus ultrasound in primary sclerosing cholangitis	seems to be the wrong population
Lee, S. and Kim, M. J. and Kim, S. and Choi, D. and Jang, K. T. and Park, Y. N. (2019), Intraductal papillary neoplasm of the bile duct: Assessment of invasive carcinoma and long-term outcomes using MRI	seems to be the wrong population
Sun, N. and Xu, Q. and Liu, X. and Liu, W. and Wang, J. (2015), Comparison of preoperative evaluation of malignant low-level biliary obstruction using plain magnetic resonance and coronal liver acquisition with volume acceleration technique alone and in combination	seems to be the wrong population (mixed population)
Yang, X. and Ren, K. and Sun, W. and Qi, X. and Wang, Y. and Chu, J. and Xu, K. (2017), 3T diffusion weighted MR imaging in diagnosing extrahepatic cholangiocarcinoma	Seems to be combined modalities

Literature search strategy
Systematic reviews

Embase.com	481	471
Medline Ovid	251	76
Total	**732**	**547**

New references: 81

Embase.com
'biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR 'bile duct') NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ab,ti,kw AND [english]/lim AND [2012-2019]/py NOT 'conference abstract':it NOT ([animals]/lim NOT [humans]/lim) AND ('systematic review'/exp OR 'meta analysis'/exp OR (((systematic*) NEAR/3 (review)) OR meta-analy* OR metaanaly*):ab,ti,kw)

Medline Ovid
exp Gallbladder Neoplasms/ or exp biliary tract neoplasms/ or exp bile duct neoplasms/ or exp cholangiocarcinoma/ or exp klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile duct) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ab,ti,kf. AND english.la. AND (2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020) NOT (exp animals/ NOT humans/) AND (Systematic Review/ OR Meta-Analysis/ OR (((systematic*) ADJ3 (review)) OR meta-analy* OR metaanaly*).ab,ti,kf.)

Trials

Database searched	**via**	**Years of coverage**	**Records**	**Records after duplicates removed**
Embase	Embase.com	1971 - Present	767	760
Medline ALL	Ovid	1946 - Present	422	80
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	643	464
Total			**1832**	**1304**

Embase 766
('biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin*):ti,kw) AND [english]/lim AND [2015-2030]/py NOT 'conference abstract':it NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) AND (('clinical trial'/exp OR (trial):ab,ti,kw) OR [clinical trial number]/lim)

Medline Ovid 422
(exp *Gallbladder Neoplasms/ or exp *biliary tract neoplasms/ or exp *bile duct neoplasms/ or exp *cholangiocarcinoma/ or exp *klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ti,kf.) AND english.la. AND 2015:2030.(sa_year). NOT (exp animals/ NOT humans/) AND ((Clinical Trial/ OR (trial).ab,ti,kf.) OR clinicaltrials.si.)

Cochrane (2015-2020) 643
((((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ti)

Module 7 – Locoregionale behandeling met TACE of SIRT voor iCCA

Uitgangsvraag
Wat is de rol van 'transarterial chemoembolization' (TACE) en 'selective internal radiation therapy' (SIRT) bij patiënten met een niet-resectabel intrahepatisch cholangiocarcinoom?

Inleiding
Slechts 17% van de patiënten met een intrahepatisch cholangiocarcinoom (iCCA) komt in Nederland in aanmerking voor chirurgische resectie (Olthof, 2023). Bij de helft van de patiënten die niet in aanmerking komen voor een resectie is de ziekte beperkt tot de lever. Bij deze patiënten met een lokaal vergevorderd iCCA (i.e. niet-resectabel) is palliatieve systemische behandeling de standaardbehandeling (hyperlink invoegen). De mediane overleving met palliatieve chemotherapie met gemcitabine-cisplatin is 17 maanden met een 3-jaars overleving van 2,8% (Lamarca, 2020).

Met alleen palliatieve systemische behandeling overlijdt ongeveer 70% van alle patiënten met iCCA *niet* aan afstandsmetastasen, maar aan progressie van ziekte in de lever met segmentele galwegobstructie, cholangitiden en/of leverfalen (Yamashita, 2017). Dit is de rationale van locoregionale behandeling van iCCA. De behandeling wordt meestal gedaan tijdens of na palliatieve systemische behandeling.

Twee verschillende locoregionale behandelingen zijn in de literatuur onderzocht: Transarterial chemoembolization (TACE) en selective internal radiation therapy (SIRT). Bij TACE worden bolletjes met chemotherapeutica toegediend, terwijl bij SIRT (radio-embolisatie) bolletjes met de radioactieve stof Yttrium-90 geïnjecteerd worden. De bolletjes komen in de levertumor met een katheter via de arteria femoralis of radialis.

Search and select
A systematic review of the literature was performed to answer the following question: What are the (un)beneficial effects of transarterial chemoembolization (TACE) and selective internal radiation therapy (SIRT) in patients with unresectable intrahepatic cholangiocarcinoma (ICC)?

P: patients with unresectable ICC
I: systemic treatment and TACE or SIRT
C: systemic treatment
O: overall survival, quality of life, local tumor control, serious adverse events

Relevant outcome measures
The working group considered overall survival as a critical outcome measure for decision making; and quality of life, local tumor control and serious adverse events as important outcome measures for decision making.

The working group defined local tumor control as stable disease, partial response or complete response, based on the Response Evaluation Criteria in Solid Tumors (RECIST). In addition, the working group defined serious adverse events as grade 3-4 toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Other outcome measures were not defined a priori.

The working group defined a minimal clinically (patient) relevant difference as follows: (using the PASKWIL criteria for palliative treatment where possible):

- Overall survival:
    - If median overall survival in control group ≤ 12 months: absolute difference in OS > 12 weeks and hazard ratio (HR) < 0.7.
    - If median overall survival in control group > 12 months: absolute difference in OS of > 16 weeks and HR < 0.7.
- Quality of life: absolute difference ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other disease-specific quality of life questionnaires;
- Local tumor control: statistically significant difference in local tumor control;
- Serious adverse events: ≥ 5% difference in lethal adverse events and ≥ 25% difference in serious (grade ≥3) adverse events

Search and select (Methods)

A broad systematic literature search was performed to identify relevant publications involving patients with biliary tract cancer. The databases Medline (via OVID) and Embase (via Embase.com) were searched for systematic reviews with relevant search terms until August 31, 2021. Medline (via OVID) and Embase (via Embase.com) were also searched until 12-01-2021 for trials with relevant search terms. The detailed search strategy is depicted under the tab Methods. The systematic literature searches resulted in 1861 hits (547 systematic reviews and 1304 RCTs).

A preselection of systematic reviews and RCTs was made by advisors from the Knowledge Institute of the Dutch Association of Medical Specialists, based on study population and study design. An inclusive approach was followed, in case of any doubt about the eligibility of a publication, the publication was included in the preselection. In total, 150 publications on locoregional therapies were included in the preselection.

Subsequently, publications were screened based on title and abstract using the following selection criteria: (a) full-text Dutch or English language publication; (b) systematic review or RCT; (c) involving patients with unresectable ICC; and (d) comparing overall survival, quality of life, local tumor control or serious adverse events between patients treated with systemic chemotherapy and TACE or SIRT and patients treated with systemic chemotherapy alone. A priori, the working group decided that observational studies included in systematic reviews should be of sufficient quality to allow for a valid GRADE assessment and to allow for drawing conclusions that can guide the recommendations. Observational studies were considered to be of sufficient quality if they: (a) compared at least two interventions; (b) included a total of at least 50 patients; and (c) corrected for at least one plausible confounder, e.g. by matching cases and controls, stratification, or statistical correction by performing a multivariable analysis.

This resulted in 12 publications for TACE and 27 publications for SIRT. After reading the full text, all studies were excluded. A table with reasons for exclusion is presented under the tab Methods. The guideline working group was aware of a systematic review and meta-analysis of locoregional treatment, including TACE and SIRT, by Edeline (2021). This review provides an overview of the outcomes of locoregional treatment. However, no comparison was made between the intervention (systemic treatment and TACE or SIRT) and comparison (systemic treatment) as described in the PICO. Results are summarized below to provide an overview of the best available evidence for TACE and SIRT. In addition, the guideline working group was aware that a randomized controlled phase II trial by Martin (2020) that was identified in our search and excluded because at the time it had only been published in abstract form.

Results

Summary of literature

Description of studies

The review by **Edeline (2021)** is summarized below. Important study characteristics and results are summarized in the evidence table.

For SIRT, characteristics of 25 studies with a total of 1,232 patients were described, of which 2 (8%) non-randomized trials, 3 (12%) prospective cohort studies, and 20 (80%) retrospective observational studies. Out of these 25 studies, 23 (92%) studies were classified as high risk of bias, and 2 (8%) studies as intermediate risk of bias. The intervention did not always match the intervention as described in the PICO (systemic treatment and SIRT). Four out of 25 studies provided data on concomitant systemic chemotherapy, which was delivered in 63 out of 221 patients (29.9%).

For TACE, 20 studies with a total of 1,145 patients were included, of which 2 (15%) non-randomized trials, 1 (5%) randomized trial, 2 (10%) prospective observational studies, and 15 (75%) retrospective observational studies. 17 (85%) studies were classified as high risk of bias, 3 (15%) studies as intermediate risk of bias, and none as low risk of bias. The intervention did not always match the intervention as described in the PICO (systemic treatment and TACE) or no details were available. Two out of 20 studies provided data on concomitant systemic chemotherapy; this was delivered in 29 out of 39 patients (74%).

Martin (2022) conducted a randomized controlled open-label phase II trial (the DELTIC trial) of patients with unresectable iCCA. Patients were randomized (1:1) to receive either irinotecan drug-eluting beads therapy (DEBIRI) by transarterial infusion with concomitant systemic gemcitabine and cisplatin (n=24) or systemic gemcitabine and cisplatin alone (n=22). Outcome measures included overall survival, response rate, and serious adverse events.

Results

Edeline (2021)

	SIRT	**TACE**
Pooled weighted mean overall **survival** months (95% CI); number of studies with data available	14.1 (12.1 to 16.0); 26	15.9 (12.9 to 19.0); 20
Quality of life	Not reported	Not reported
Local tumor control Pooled **response rate** % (95% CI); heterogeneity I^2-p value; number of studies with data available	23.4 (15.7 to 31.9); 85.0%-<0.001; 18	26.3 (14.0 to 40.6); 92.8%-<0.001; 15
Serious adverse events	Not reported	Not reported

Martin (2022)

Overall survival

Median overall survival was 33.7 months (95%CI 13.5 to 54.5 months) for patients who received DEBIRI with gemcitabine and cisplatin and 12.6 months (95% CI 8.7 to 33.4 months) for patients who received gemcitabine and cisplatin alone (p=0.048). This difference was probably clinically relevant as the absolute difference between groups was more than 16 weeks, however no hazard ratio was reported.

Quality of life
Martin (2022) did not report on quality of life.

Response rate
The overall response rate at two months (86% versus 56%; p=0.02), four months (77% versus 50%; p=0.03), and six months (69% versus 42%; p<0.05) months was significantly higher in patients who received DEBIRI with gemcitabine and cisplatin compared with patients who received gemcitabine and cisplatin alone. The 12-month response was 50% in patients who received DEBIRI with gemcitabine and cisplatin and 24% in patients who received gemcitabine and cisplatin alone (p=0.02). These differences were clinically relevant.

Serious adverse events
The incidence of serious adverse events was comparable between the groups: 34% of patients who received DEBIRI with gemcitabine and cisplatin experienced a grade 3 or 4 adverse event compared with 36% of patients who received gemcitabine and cisplatin alone.

Level of evidence of the literature

The evidence from the review by Edeline (2021) could not be assessed using the GRADE approach, because no direct comparison was made between the intervention and control as described in the PICO.

The evidence derived from the RCT by Martin (2022) started at 'high' for all outcomes.

The level of evidence regarding the outcome measure **overall survival** was downgraded by three levels because of study limitations (-1; risk of bias because of a lack of information about the randomization and allocation procedure and industry involvement) and number of included patients (-2; imprecision because of the broad confidence intervals including the possibility of no clinically relevant effect or a clinically relevant effect in favor of the control group).

The level of evidence regarding the outcome measure **response rate** was downgraded by two levels because of study limitations (-1; risk of bias because of a lack of information about the randomization and allocation procedure and industry involvement) and number of included patients (-1; imprecision because the sample size does not meet the optimal information size).

The level of evidence regarding the outcome measure **serious adverse events** was downgraded by three levels because of study limitations (-1; risk of bias because of a lack of information about the randomization and allocation procedure and industry involvement) and number of included patients (-2; imprecision because the sample size does not meet the optimal information size).

Conclusions

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of TACE combined with systemic treatment on **overall survival** when compared with systemic treatment alone in patients with unresectable ICC. *Source: Martin, 2022*

Quality of life

NO GRADE	No comparative studies were identified regarding the effect of TACE or SIRT combined with systemic treatment on **quality of life** when compared with systemic treatment alone in patients with unresectable ICC. *Source: Edeline, 2021*

Local tumor control (response rate)

Low GRADE	TACE combined with systemic treatment may increase **response rate** when compared with systemic treatment alone in patients with unresectable ICC. *Source: Martin, 2022*

Serious adverse events

Very low GRADE	The evidence is very uncertain about the effect of TACE combined with systemic treatment on **serious adverse events** when compared with systemic treatment alone in patients with unresectable ICC. *Source: Martin, 2022*

Overwegingen – van bewijs naar aanbeveling

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

Met alleen palliatieve systemische behandeling overlijdt ongeveer 70% van alle patiënten met intrahepatisch cholangiocarcinoom (iCCA) *niet* aan afstandsmetastasen, maar aan progressie van ziekte in de lever met segmentele galwegobstructie, cholangitiden en/of leverfalen (Yamashita, 2017). Dit is de rationale voor locoregionale behandeling – tijdens of na palliatieve behandeling – voor patiënten met iCCA die niet in aanmerking komen voor een resectie. Deze rationale lijkt het sterkst voor patiënten met een grote tumor dichtbij de leverhilus zonder (klachten van) metastasen buiten de lever.

Fase 3 studies die systemische therapie met of zonder locoregionale therapie voor iCCA vergelijken waren (nog) niet gepubliceerd in 2023. Een systematische review (Edeline, 2021) presenteert een overzicht van de uitkomsten van 5 locoregionale behandelingen, waaronder ‘transarterial chemoembolization’ (TACE) en ‘selective internal radiation therapy’ (SIRT).

Voor TACE werden 20 studies geïncludeerd, waaronder 15 retrospectieve studies en 5 prospectieve studies. In de enige gerandomiseerde fase II trial (DELTIC trial, n=48) werd een directe vergelijking gemaakt tussen systemische chemotherapie met of zonder TACE (Martin, 2020). Patiënten die naast systemische chemotherapie (gemcitabine/cisplatin) ook TACE kregen, hadden een langere mediane overleving (33,7 vs. 12,6 maanden; p=0.048) (zeer lage bewijskracht), en een hogere response rate na zes maanden (69% vs 42%, p<0.05)

(lage bewijskracht), vergeleken met patiënten die alleen systemische chemotherapie ontvingen. Ernstige bijwerkingen (graad 3-4) waren vergelijkbaar in beide groepen (zeer lage bewijskracht). Er werden geen data voor kwaliteit van leven gepresenteerd.

Voor SIRT werden 25 studies geïncludeerd, waaronder 20 retrospectieve studies en 5 prospectieve studies. Geen van de studies was gerandomiseerd. De MISPHEC-trial was een niet-gerandomiseerde fase II trial met 41 patiënten die gelijktijdig eerstelijns palliatieve chemotherapie en SIRT kregen (Edeline, 2020). De RECIST response rate was 39%. De mediane overleving was 22 maanden en de overleving na 3 jaar was ongeveer 40%. De MISPHEC leidde tot de gerandomiseerde SIRCCA-trial (NCT02807181), die voortijdig is beëindigd na inclusie van 89 patiënten en nog niet is gepubliceerd.

De standaard zorg en daarmee de benchmark voor locoregionale behandeling zijn de resultaten van de ABC-trials. Patiënten met niet-resectable iCCA (zonder metastasen) die gemcitabine met cisplatin kregen hadden een mediane overleving van 17 maanden met een 3-jaars overleving van 2,8% (Lamarca, 2020). De systematische review vond een mediane overleving na TACE en SIRT die vergelijkbaar was met alleen systemische behandeling (Edeline, 2021). Echter, de 3-jaars overleving in de twee prospectieve studies was aanzienlijk hoger na SIRT of TACE (Martin, 2020; Edeline, 2020).

De betere response rate en overleving met aanvullende locoregionale behandeling in de DELTIC en MISPHEC trials zijn dus veelbelovend. Echter, de bewijskracht is op dit moment onvoldoende om locoregionale behandeling als aanvullende standaard zorg aan te bevelen. Toekomstige studies moeten een klinisch relevante en statistisch significante verbetering in overleving laten zien in fase 3 trials. Of tenminste een consistente en robuuste verbetering in 3-jaars overleving in fase 2 trials.

Twee andere locoregionale behandeling (percutane ablatie en externe radiotherapie) zijn in deze module niet onderzocht. Ablatie en radiotherapie zijn zelden een behandeloptie, omdat de diameter van iCCA meestal te groot is. Ablatie kan wel overwogen worden bij afwijkingen kleiner dan 3 cm, die meestal gevonden worden tijdens surveillance voor hepatocellulair carcinoom in patiënten met levercirrose.

Tenslotte, de literatuur voor hepatic arterial infusion pump (HAIP) chemotherapy met floxuridine is in deze module ook niet onderzocht. Bij HAIP wordt middels een operatie een katheter geplaatst in een zijtak van de lever slagader. Deze katheter is verbonden met een onderhuidse pomp met chemotherapie (floxuridine). Floxuridine lijkt op 5-FU, maar kan in zeer hoge dosis worden toegediend omdat het vrijwel volledig door de lever wordt gemetaboliseerd. HAIP wordt veel toegepast in de VS, maar floxuridine is in de EU in 2023 nog niet geregistreerd. Een meta-analyse van 9 studies, inclusief 3 fase II trials, vond een mediane overleving van 29 maanden een 3-jaars overleving van 40% (Holster, 2022). Een lopende fase III trial (NCT04891289) vergelijkt gemcitabine met oxaliplatin/cisplatin en HAIP chemotherapie versus alleen gemcitabine met oxaliplatin/cisplatin.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
Het belangrijkste doel van locoregionale behandeling is levensverlenging met behoud van kwaliteit van leven. De kans op complicaties en de bijwerkingen zijn beperkt. De behandeling is vaak eenmalig.

Kosten (middelenbeslag)
Omdat de effectiviteit nog onzeker is, is het moeilijk om de kosteneffectiviteit vast te stellen. Als locoregionale behandeling daadwerkelijk de 3-jaars overleving kan verlengen van 2,8% naar ongeveer 40%, zoals een fase II studie voor SIRT en een meta-analyse voor HAIP chemotherapie laten zien, dan zal locoregionale behandeling zeer waarschijnlijk kosteneffectief zijn.

Aanvaardbaarheid, haalbaarheid en implementatie
Locoregionale behandeling van lokaal-uitgebreid iCCA lijkt aanvaardbaar en haalbaar, als in de toekomst beter bewijs komt voor de effectiviteit. Van de ongeveer 200 patiënten per jaar met iCCA zouden hooguit ongeveer 80 patiënten hiervoor in aanmerking komen; de andere patiënten komen in aanmerking voor chirurgische resectie of hebben gemetastaseerde ziekte buiten de lever. De zorg voor patiënten met iCCA is gecentraliseerd in de 7 academische ziekenhuizen waar locoregionale behandeling beschikbaar is voor andere levertumoren zoals hepatocellulair carcinoom. De aanbevelingen zijn in overeenstemming met de huidige zorg.

Aanbeveling
Aanbeveling-1
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
De aanvullende waarde van locoregionale therapie voor patiënten met lokaal-uitgebreid iCCA is onzeker. De rationale van locoregionale progressie als belangrijkste doodsoorzaak is sterk. Locoregionale therapie heeft mogelijk een betere response rate en overleving, met name na 3 jaar. Echter, het best beschikbare bewijs bestaat slechts uit 1 kleine gerandomiseerde fase II trial met TACE en een niet-gerandomiseerde fase II trial met SIRT.

Verricht geen standaard locoregionale therapie voor patiënten met lokaal-uitgebreid iCCA.

Overweeg locoregionale therapie (TACE of SIRT) voor patiënten met lokaal-uitgebreid iCCA als sprake is van een grote tumor dichtbij de leverhilus met dreigende galwegobstructie bij voorkeur in studieverband.

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Bijlagen bij module 7 Locoregionale behandeling met TACE of SIRT voor iCCA

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

Research question: What are the (un)beneficial effects of transarterial chemoembolization (TACE) and selective internal radiation therapy (SIRT) in patients with unresectable intrahepatic cholangiocarcinoma (ICC)?

Study reference	Study characteristics	Patient characteristics	SIRT	TACE	Follow-up	Outcome measures and effect size	Comments
Edeline, 2021 PS., study characteristics and results are extracted from the SR	SR and meta-analysis of (mostly retrospective) cohort studies *Literature search up to October/November 2020* **SIRT (26 studies)** **A**: Helmberger, 2020 **B**: Azar, 2020 **C**: Bargellini, 2020 **D**: Buettner, 2020 (two cohorts: resin and glass) **E**: Filippi, 2020 **F**: Köhler, 2019 **G**: Edeline, 2020 **H**: White, 2019 **I**: Bourien, 2019	Inclusion criteria SR: - studies involving patients treated for intrahepatic cholangiocarcinoma not amenable to surgery; - treated with locoregional therapies, including radioembolisation (SIRT), transarterial chemo-embolisation (TACE), hepatic arterial infusion (HAI) of chemotherapy, external beam radiotherapy	Glass-microspheres were used in 7 of 24 cohorts, resin-microspheres in 12, and mixed in 5. A mean of 1.3 sessions were performed (data from 12 cohorts). Radioactive activity data were provided for 12 cohorts, but tumour dose only in 4. Concomitant systemic chemotherapy was delivered in 63 of 221 (29.9%) patients (data from 4 cohorts).	Lipiodol (i.e., conventional TACE) was used in 7 of 19 studies, drug-eluting beads in 6, other or mixed in 6. Embolisation was performed without chemotherapy (i.e. transarterial embolisation) in 2 of 22 cohorts, anthracycline single-agent in 3; platinum single-agent in 2, multidrug in 6, mixed regimen in 9. A mean of 3.0 sessions was delivered. Concomitant systemic chemotherapy was delivered in 29 of 39 (74.4%) patients (data only from 2	<u>End-point of follow-up</u>: Not reported <u>For how many participants were no complete outcome data available?</u> Not reported	<u>Overall survival</u> Pooled weighted mean overall survival in months (95%CI); number of studies with data available SIRT: 14.1 (12.1 to 16.0); 26 TACE: 15.9 (12.9 to 19.0); 20 <u>Local tumor control</u> Pooled weighted mean progression-free survival in months (95%CI); number of studies with data available SIRT: 7.8 (4.6 to 11.0); 8 TACE: 15.0 (4.4 to 25.6); 7 Pooled weighted mean liver progression-free survival in months (95%CI); number of studies with data available SIRT: 4.9 (0.8 to 9.2); 3 TACE: 4.9 (0 to 43.0); 2	<u>Review authors' conclusions</u> Available literature on LRT for iCC was heterogeneous and of insufficient quality to make strong recommendations. The results of the only randomised trial included in this systematic review, comparing gemcitabine-cisplatin combined with TACE using irinotecan-loaded drug-eluting beads with gemcitabine-cisplatin alone are promising: there was significantly more downsizing with resection/ablation in the TACE arm (25% vs 8%, P less than 0.005), and improved OS (33.7 vs 12.6 months, p = 0.048) [Martin, 2020].

	J: Gangi, 2018 **K:** Shaker, 2018 **L:** Reimer, 2018 **M:** Akinwande, 2017 **N:** Swinburne, 2017 **O:** Jia, 2017 **P:** Soydal, 2016 **Q:** Saxena, 2010 **R:** Bailly, 2019 (abstract only) **S:** Mehta, 2019 (abstract only) **T:** Todica, 2017 (abstract only) **U:** Shridhar, 2017 (abstract only) **V:** Schatka, 2017 (abstract only) **W:** Wang, 2016 (abstract only) **X:** Mulit Jogi, 2015 (abstract only) **Y:** Saffouri, 2015 (abstract only) **Z:** Bower, 2013 (abstract only) **TACE (20 studies)** **A:** Zhou, 2020 **B:** Luo, 2020 **C:** Ge, 2020 (two modalities) **D:** Goerg, 2019 **E:** Wright, 2018 **F:** Akinwande, 2017 **G:** Aliberti, 2017 **H:** Hyder, 2013 (three cohorts)	(EBRT) and ablation; - studies available in PubMed and/or Embase from January 2000 to the date of search. Exclusion criteria SR: - studies including patients with all types of BTC without distinction of outcomes for iCC, studies pooling results of different LRT without distinction of outcomes for each of them; - studies with number of patients less than 10; - studies including patients with resected tumours or resectable patients treated with a neoadjuvant strategy; - studies published in a language other than English;		cohorts).		Pooled response rate % (95%CI); number of studies with data available SIRT: 23.4 (15.7 to 31.9); 18 TACE: 26.3 (14.0 to 40.6); 15 Pooled secondary resection rate % (95%CI); number of studies with data available SIRT: 7.6 (3.7 to 12.5); 8 TACE: 12.7 (6.4 to 20.3); not reported	However, the limited number of patients included (n = 48) will not be sufficient to derive a strong recommendation. The interpretation of this pooled analysis is limited by the large heterogeneity of the results, illustrated by wide CIs and significant tests for heterogeneity (with the notable exception of complete response rates after ablation). This might be related to the heterogeneity of the population targeted between studies, thus accounting for inter-study heterogeneity. The treatment modalities were studied in different populations. For this reason, results have not been compared between modalities. Also, for each treatment modality, studies varied greatly in the population included. Prospective evidence (in particular from randomized controlled trials) for the use of LRT in the treatment of patients with iCC is an area of unmet need. Future research seems justified by the

	I: Scheuermann, 2013 **J:** Vogl, 2012 **K:** Park, 2011 **L:** Kiefer, 2011 **M:** Schiffman, 2011 **N:** Shitara, 2008 **O:** Gusani, 2008 **P:** Martin, 2020 (abstract only) **Q:** Fitschek, 2018 (abstract only) **R:** Ogasaware, 2017 (abstract only) **S:** Dedes, 2016 (abstract only) **T:** Zhang, 2015 (abstract only) <u>Source of funding:</u> COST (European Cooperation in Science and Technology) <u>Conflicts of interest:</u> several reported	- studies not reporting at least one of the following outcomes: radiological response by (RECIST) v1.1, progression-free survival , liver-specific-PFS, OS, and grade 3–4 toxicity according to NCI-CTCAE. 93 studies including 101 cohorts were included - SIRT: 27 cohorts (1232 patients) - TACE: 22 cohorts (1145 patients) *N patients per cohort, median (range)* SIRT: 29 (16-125) TACE: 35 (11-183) *Age, mean (range of means)* SIRT: 64 (55-76) TACE: 62 (59-75) *Sex, % male* SIRT: 478/966 (49%) TACE: 502/918 (55%)					encouraging results presented here. Future phase III clinical trials should be adequately powered to detect clinically relevant differences in survival. An international collaborative effort is necessary to make these trials possible.

		ECOG PS 0 SIRT: 340/665 (51%) TACE: 112/241 (47%)					

Evidence table for intervention studies

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison/control (C)	Follow-up	Outcome measures and effect size	Comments
Martin (2022) (DELTIC trial)	Type of study: Multicenter, open-label, randomized phase II trial Setting and country: Multicenter study, USA Source of funding: University of Louisville Division of Surgical Oncology. FDA: IDE Submission # NCT01648023 Conflicts of interest: Partial funding for this trial came from both BTG/Biocompatibles and Boston Scientific. None of the authors have	Patients with unresectable intrahepatic cholangiocarcinoma Inclusion criteria: - Over 18 years of age; - unresectable, histologically proven cholangiocarcinoma to the liver; - chemotherapy naive for their disease; - liver-dominant disease (defined as ≥ 80% tumor body burden confined to the liver) but less than 60% liver replacement by tumor; - Eastern Cooperative Oncology Group	Irinotecan drug-eluting beads (DEBIRI) therapy by transarterial infusion in combination with systemic gemcitabine and cisplatin DEBIRI is performed through a femoral or axillary artery puncture after appropriate anatomic identification of the right and left hepatic arteries. One vial of beads is loaded with 100 mg of irinotecan chemotherapy and administered through the arterial puncture. Treatment is performed using a lobar approach, based on the extent and distribution of the disease, with most treatments performed in the outpatient setting. Cisplatin at 25 mg/m^2 was given as a 2-h intravenous infusion on days 1 and 8.	Systemic gemcitabine and cisplatin Cisplatin at 25 mg/m^2 was given as a 2-h intravenous infusion on days 1 and 8. Starting in week 2, gemcitabine was given at 1000 mg/m^2 as a 30-min IV infusion following cisplatin on days 1 and 8, also starting in week 2.	Length of follow-up: Median follow-up of 29 months (range 27-48 months) Loss to follow-up or missing outcome data: In both groups, two patients did not receive the allocated intervention/control treatment. In the control group, 1 patient was lost to follow-up but was included in the analysis.	*Overall survival* Months, median (95%) I: 33.7 (13.5 to 54.5) C: 12.6 (8.7 to 33.4) p=0.048 *Overall response rate* Two months I: 86% C: 56% P=0.02 Four months I: 77% C: 50% P=0.03 Six months I: 69% C: 42% P<0.05 *Serious adverse events (toxicity grade ≥ 3)* I: 34% C: 36%	Authors conclusion: Combination Gem/Cis with DEBIRI is safe, and leads to significant improvement in downsizing to resection, improved progression-free survival, and overall survival. On the basis of molecular profiling, patients with unresectable liver-dominant ICC should be considered for concurrent hepatic arterial therapy with optimal systemic chemotherapy.

	conflicts to declare.	Performance Status score of ≤ 2 <u>Exclusion criteria:</u> - eligibility for curative treatment (i.e., resection or radiofrequency ablation) <u>N total at baseline:</u> Randomized: N = 46 I: N = 24 C: N = 22 <u>Important characteristics:</u> Age, median P=0.09 Sex, n/N (%) male: I: 12/24 (50%) C: 8/22 (36%) Performance status 0 I: 16/24 (67%) C: 12/22 (55%) 1 I: 8/24 (33%) C: 10/22 (45%) 2 I: 0/24 (0%) C: 0/22 (0%) Extent of liver involvement median	Starting in week 2, gemcitabine was given at 1000 mg/m^2 as a 30-min IV infusion following cisplatin on days 1 and 8, also starting in week 2.				

		I: 35% C: 38% Presence of extrahepatic disease I: 29% C: 14% Groups were comparable at baseline.					

Risk of bias assessment of intervention studies (randomized controlled trials)

Study reference	**Was the allocation sequence adequately generated?**[a] Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?**[b] Definitely yes Probably yes Probably no Definitely no	**Was knowledge of the allocated interventions adequately prevented?**[c] **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?**[d] Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?**[e] Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?**[f] Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure**[g] LOW SOME CONCERNS HIGH
Martin (2022)	No information	No information	Definitely no; Reason: open-label design	Probably yes; Reason: in both groups, two patients did not receive the allocated intervention / control and were not included in the analysis. One patient in the control group was lost to follow-up but was included in the analysis.	Probably yes; Reason: the outcome measures listed in the methods section are all reported in the results section. Response rates and overall survival are mentioned in the trial registration.	Probably no; The study was partially funded by BTG Biocompatibles and Boston Scientific. The role of the sponsor was not described.	Some concerns (overall survival, response rate, serious adverse events)

Implementatieplan bij module 7 Locoregionale behandeling met TACE of SIRT voor iCCA

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Verricht geen standaard locoregionale therapie voor patiënten met lokaal-uitgebreid iCCA. Overweeg locoregionale therapie (TACE of SIRT) voor patiënten met lokaal-uitgebreid iCCA als sprake is van een grote tumor dichtbij de leverhilus met dreigende galwegobstructie bij voorkeur in studieverband.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn	Wetenschappelijke verenigingen	

Table of excluded studies for TACE

Author and year	Reason for exclusion
Aliberti, 2017	wrong study design (no comparison cohort)
Boehm, 2015	systematic review which excluded studies where patients received concomitant systemic chemotherapy
Dadduzio, 2018	Abstract only, wrong study design (no comparison cohort)
Luo, 2020	wrong study design (no comparison cohort)
Martin, 2020	randomized phase II trial in abstract form
Ray, 2013	systematic review of studies without a comparison cohort, a comparison not according to the PICO an studies published in abstract form only
Schicho, 2017	wrong study design (no comparison cohort)
Seidensticker, 2016	wrong study design (evaluation of individualized treatment algorithm)
Simo, 2016	broad systematic review including only a few paragraphs about TACE
Sommer, 2016	review of reviews, did not yield any relevant reviews
Yang, 2015	systematic review of studies without a comparison cohort or a comparison not according to the PICO
ChiCTR1900022856, 2019	trial register

Table of excluded studies for SIRT

Author and year	Reason for exclusion
Abeysinghe, 2018	wrong study design: case report
Al-Adra, 2015	systematic review of studies without a comparison cohort or a comparison not according to the PICO
Bargellini, 2020a	wrong study design, comparison not according to PICO
Bargellini, 2020b	Editorial
Boehm, 2015	systematic review which excluded studies where patients received concomitant systemic chemotherapy
Bourien, 2019	wrong study design (no comparison cohort)
Buettner, 2020	wrong study design (no comparison cohort)
Cucchetti, 2017	systematic review of studies without a comparison cohort or a comparison not according to the PICO
Dadduzio, 2018	Abstract only, wrong study design (no comparison cohort)
Edeline, 2020	wrong study design (no comparison cohort)
Filippi, 2017	narrative review
Gangi, 2018	wrong study design (no comparison cohort)
Jung, 2019	narrative review
Koehler, 2019	Abstract only
Köhler, 2020	wrong study design (no comparison cohort)
Levillain, 2019	wrong study design (no comparison cohort)
Najran, 2017	narrative review
Nezami, 2019	wrong study design (no comparison cohort)
Seidensticker, 2016	wrong study design (evaluation of individualized treatment algorithm)
Simo, 2016	broad systematic review including only a few paragraphs about SIRT
Sommer, 2016	review of reviews, did not yield any relevant reviews
Teo, 2015	wrong study population (primary and secondary liver malignancies, mostly HCC)
Wang, 2017	narrative review

White, 2019	wrong study design (no comparison cohort)
Yang, 2015	systematic review of studies without a comparison cohort or a comparison not according to the PICO
Zhen, 2019	systematic review not including a comparison according to the PICO
ChiCTR1900021862, 2019	trial register

Literature search strategy for systematic reviews

Embase (via Embase.com)

'biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR 'bile duct') NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ab,ti,kw AND [english]/lim AND [2012-2019]/py NOT 'conference abstract':it NOT ([animals]/lim NOT [humans]/lim) AND ('systematic review'/exp OR 'meta analysis'/exp OR (((systematic*) NEAR/3 (review)) OR meta-analy* OR metaanaly*):ab,ti,kw)

481 hits

Medline (via OVID)

exp Gallbladder Neoplasms/ or exp biliary tract neoplasms/ or exp bile duct neoplasms/ or exp cholangiocarcinoma/ or exp klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile duct) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ab,ti,kf.
AND english.la.
AND (2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020)
NOT (exp animals/ NOT humans/)
AND (Systematic Review/ OR Meta-Analysis/ OR (((systematic*) ADJ3 (review)) OR meta-analy* OR metaanaly*).ab,ti,kf.)

251 hits

Literature search strategy for RCTs

Embase (via Embase.com)

('biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin*):ti,kw) AND [english]/lim AND [2015-2020]/py NOT 'conference abstract':it NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) AND (('clinical trial'/exp OR (trial):ab,ti,kw) OR [clinical trial number]/lim)

766 hits

Medline (via OVID)

(exp *Gallbladder Neoplasms/ or exp *biliary tract neoplasms/ or exp *bile duct neoplasms/ or exp *cholangiocarcinoma/ or exp *klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR

klatskin).ti,kf.) AND english.la. AND 2015:2020.(sa_year). NOT (exp animals/ NOT humans/) AND ((Clinical Trial/ OR (trial).ab,ti,kf.) OR clinicaltrials.si.)

422 hits

Cochrane Central Register of Controlled Trials (via Wiley)
((((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ti)

643 hits

Module 8 Preoperatieve vena porta embolisatie

Uitgangsvraag
Welke patiënten met galwegkanker moeten preoperatief een vena porta embolisatie ondergaan?

Inleiding
Wanneer bij een grote leverresectie voor galwegkanker een te kleine leverrest in de patiënt achterblijft bestaat er een grote kans op het ontstaan van postoperatief leverfalen met een zeer hoge mortaliteit. Vena portae embolisatie (VPE) is een techniek waarbij door het pre-operatief afsluiten van de portale vaten van het te verwijderen deel van de lever een toename van het volume en de functie geïnduceerd wordt van de toekomstige leverrest. Hierdoor wordt het mogelijk om resectie te verrichten bij patiënten die een te kleine toekomstige leverrest hebben om veilig geopereerd te worden. Omdat VPE een techniek is die zelf ook potentieel tot complicaties, zoals bloeding, trombose en infectie en zelfs mortaliteit kan leiden is het belangrijk om te weten welke patiënten voordeel hebben van deze ingreep en welke niet.

Search and select
A systematic review of the literature was performed to answer the following question:
What are the effects of a preoperative portal vein embolization on the post-surgery 90-day mortality, quality of life, and post-surgery complications in patients with a confirmed perihilar or intrahepatic cholangiocarcinoma when compared to a situation where patients do not receive a preoperative portal vein embolization?

P: Patients with a confirmed perihilar or intrahepatic cholangiocarcinoma
I: Portal vein embolization before surgery
C: No portal vein embolization before surgery
O: Resection rate, post-operative mortality (90-day), post-operative complications, post-operative liver failure

<u>Relevant outcome measures</u>
The guideline development group considered resection rate and mortality as a critical outcome measure for decision making; and complications as important outcome measures for decision making.

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

The working group defined the following minimal clinically (patient) relevant differences:
- >2% absolute difference for 90-day post-operative mortality.
- >5% absolute difference for resection rate.
- >5% difference for post-operative complications, including lethal complications (such as liver failure).

<u>Search and select (Methods)</u>
The databases Medline (via OVID) and Embase (via Embase.com) were searched for systematic reviews with relevant search terms until 31-08-2021. Medline (via OVID) and Embase (via Embase.com) were also searched until 12-01-2021 for trials with relevant search terms. The detailed search strategy is depicted under the tab Methods. The systematic literature searches resulted in 1861 hits.

A preselection of potentially relevant literature for sections of the guideline was made by the guideline methodologists supporting the working group, excluding all obvious non-relevant articles for this section. When in slightest doubt the literature remained in the preselection. This resulted in the preselection of 316 hits from the total of 1861 hits. Thereafter, 7 studies were initially selected based on title and abstract screening by members of the working group. Studies were eligible for inclusion based on the following criteria; patients had a confirmed perihilar or intrahepatic cholangiocarcinoma, preoperative portal vein embolization was compared to a situation without preoperative portal vein embolization, at least one of the outcomes of interest was reported. Systematic reviews that included eligible (non)randomized comparative studies were selected. Primary studies needed to have a randomized comparative design to be selected for this guideline module. Primary non-randomized studies were excluded from the literature analysis when not included in a systematic review. After reading the full text, 6 studies were excluded (see the table with reasons for exclusion under the tab Methods), and one systematic review was further assessed (Glantzounis, 2017).

Glantzounis (2017) performed a systematic review to gather information about the effect of preoperative portal vein embolization in the surgical management of patients with primary liver or biliary cancer. A search was conducted in PubMed and the Cochrane Library with the search period limited from the 1st of January 1990 to the 30th of September 2015. Studies were selected when concerning portal vein embolization and hepatobiliary tumors and when assessing clinical parameters of interest (patient characteristics, indications for PVE, technique and materials, success rate, complications, morbidity, mortality, survival). Studies were excluded when they were case reports or case studies with less than 10 participants, non-English, or animal studies. Furthermore, studies were excluded when patients underwent portal vein embolization solely for metastases. Studies with mixed populations were included when there were at least 10 patients with primary liver cancer. Risk of bias of the included studies was not presented. From 40 included studies, 12 non-randomized studies specifically concerned patients with primary biliary cancer. Two of these studies (Hong, 2011; Kang, 2013) eventually met the previously mentioned eligibility criteria for the literature analysis in the current guideline module, while the other 10 studies did not match our eligibility criteria (see the table with reasons for exclusion under the tab Methods).

Results

Two non-randomized studies (Hong, 2011; Kang, 2013) identified by a previously published systematic review (Glantzounis, 2017) were included for the literature analysis. Our initial search strategy in Medline (via OVID) and Embase (via Embase.com) did not identify any additional relevant trials or systematic reviews after the search date of Glantzounis (2017). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Hong (2011) selected patients from a Korean hospital database scheduled for a right extended hemihepatectomy for pCCA and divided the groups by whether the patient had received preoperative portal vein embolization or not. Exclusion criteria were not described. Thirty-five patients were selected of whom 14 received preoperative portal vein embolization (PVE-group) and 21 did not (non-PVE-group). An interventional radiologist used a percutaneous transhepatic ipsilateral approach to access the right portal vein under ultrasound guidance to perform a preoperative portal vein embolization. Portography was used to assess the portal vein anatomy, whereafter the portal vein was embolized. Several

embolic materials were used for embolization, such as a gelatine sponge, thrombin, coil, or polidocanol. Thirteen patients received a right portal vein embolization, while one patient received a right portal vein embolization including a segment 4 portal vein branches embolization. Fourteen patients received a right liver resection (hemihepatectomy: n=4, trisectionectomy: n=10) after embolization (time interval not specified). The PVE-group (8 males, 6 females) had a median age of 62 years (range: 49-76). Twelve patients (12/14, 86%) received preoperative biliary drainage in the PVE-group. The non-PVE-group received a right liver resection only (hemihepatectomy: n=4, trisectionectomy: n=17), without PVE. This non-PVE-group group (9 males, 12 females) had a median age of 58 years (range: 37-72). Fifteen patients (15/21, 71%) in the non-PVE-group required preoperative biliary drainage. No corrections for possible confounders were applied.

Kang (2013) selected patients undergoing a partial hepatectomy for pCCA between 2005 and 2010 with a future liver remnant of ≤30% from a Korean hospital database. Patients undergoing left extended hepatectomies were excluded. Groups were divided by whether the patient received preoperative right portal vein embolization (PVE-group, n=11) or not (non-PVE-group, n=22). In the PVE-group, the mean age was 65.4 years (SD: 10.3) with a sex ratio of 1.2:1 (M:F). Patients in this group had either a Bismuth type IV (n=9, 81.8%) or type IIIa (n=2, 18.2%) and all received biliary drainage. The initial future liver remnant was 20.8% (SD: 4.3) in the PVE-group. Patients with preoperative right portal vein embolization underwent either a right trisectionectomy (n=6, 54.5%) or an extended right hemihepatectomy (n=5, 45.5%). The non-PVE-group had a mean age of 64.6 years (SD: 4.4) and a male to female ratio of 2.7:1. The observed Bismuth classification wat either type IV (n=4, 18.2%) or type IIIa (n-18, 81.8%), while 18 patients (81.8%) received biliary drainage. The initial future liver remnant was 22.4% (SD: 3.6). Patients in the non-PVE-group received either a right trisectionectomy (n=2, 9.1%) or an extended right hemihepatectomy (n=20, 90.9%). The exact difference between extended right resection and a trisectionectomy is not exactly stated but probably refers to an anatomical (including complete S4) vs non-anatomical (partial S4) resection. No corrections for possible confounders were applied.

Results

Resection rate

Hong (2011) reviewed patient records and selected patients that underwent a right extended hemihepatectomy and thus all patients in the study received a resection. Kang (2013) selected patients undergoing right extended hepatectomy with a FLR≤30% for their study. Therefore, all patients received a resection.

Post-operative 90-day mortality

Hong (2011) reported the mortality after surgery. In the preoperative PVE-group, three deaths (3/14, 21.4%) were observed within 90 days post-surgery. Two deaths (2/21, 9.5%) were observed after surgery in the group which had not received preoperative PVE. All patients died because of liver failure.

Kang (2013) reported only in-hospital mortality after surgery. All eleven patients who received a PVE received surgery. Two patients (2/11, 18.2%) who received a PVE died (myocardial infarct: n=1, liver failure: n=1). No patients (0/22, 0%) without PVE had an in-hospital death. From this data we performed a Chi^2 test (p=0.04).

Post-operative complications

Post-surgery complications were reported by Kang (2013). Intra-abdominal bleeding was observed in 4 patients who received a preoperative PVE (36.4%) compared to 3 patients in the group not receiving a preoperative PVE (13.6%). Postoperative bleeding was observed in 1 patient with preoperative PVE (9.1%) compared to 2 patients without embolization (9.1%). Sepsis was observed in 2 patients receiving preoperative embolization (18.2%) compared to 1 patient in the group not receiving embolization (4.5%).
Overall, the postoperative morbidity rate in the PVE-group was 64% (7/11) compared to 32% (7/22) in the non-PVE group (p=0.136).

Post-operative liver failure
Liver failure seemed to be reported as a cause of death in the studies, not as an event for the overall incidence of liver failure in the sample.
Hong (2011) reported for three patients (3/14, 21%) in the embolization group that liver failure occurred (as the cause of their death), compared to two patients (2/21, 10%) in the non-embolization group. From this data we performed a Chi^2 test (p=0.32).
Kang (2013) only reported liver failure (as a cause of death) for one patient in the embolization-group (1/11, 9%).

Level of evidence of the literature
GRADE starts on 'LOW' when the body of evidence contains observational studies due to a serious risk of selection bias.

The level of evidence regarding the outcome measure resection rate was downgraded by 4 levels because of applicability (2 level for indirectness: patients were selected for the study when they had received a resection thus all patients received a resection); number of included patients (2 levels for imprecision: low number of participants); publication bias was not assessed (not graded, reason: less than 10 studies included in the body of evidence).

The level of evidence regarding the outcome measure (90-day) mortality was downgraded by 2 levels because of study limitations; number of included patients (2 levels for imprecision: low number of participants causing very wide confidence intervals); publication bias was not assessed (not graded, reason: less than 10 studies included in the body of evidence).

The level of evidence regarding the outcome measure post-operative complications was downgraded by 3 levels because of study limitations (1 levels for risk of bias: there is probably a lack of blinding of patients and healthcare providers [the latter possibly also being the outcome assessors]); number of included patients (2 levels for imprecision: low number of participants); publication bias was not assessed (not graded, reason: less than 10 studies included in the body of evidence).

The level of evidence regarding the outcome measure post-operative liver failure was downgraded by 3 levels because of study limitations (1 levels for risk of bias: there is probably a lack of blinding of patients and healthcare providers [the latter possibly also being the outcome assessors]); number of included patients (2 levels for imprecision: low number of participants); publication bias was not assessed (not graded, reason: less than 10 studies included in the body of evidence).

Conclusions

VERY LOW GRADE	The evidence is very uncertain about the effect of PVE before surgery on the **post-operative 90-day mortality** in patients with a perihilar or intrahepatic cholangiocarcinoma, when compared to no PVE before surgery. *Sources: Hong, 2011; Kang, 2013*

VERY LOW GRADE	The evidence is very uncertain about the effect of PVE before surgery on the **resection rate** in patients with a perihilar or intrahepatic cholangiocarcinoma, when compared to no PVE before surgery. *Sources: Hong, 2011; Kang, 2013*

VERY LOW GRADE	The evidence is very uncertain about the effect of PVE before surgery on the **post-surgery complications** in patients with a perihilar or intrahepatic cholangiocarcinoma, when compared to no PVE before surgery. *Sources: Kang, 2013*

VERY LOW GRADE	The evidence is very uncertain about the effect of PVE before surgery on the **post-operative liver failure** in patients with a perihilar or intrahepatic cholangiocarcinoma, when compared to no PVE before surgery. *Sources: Hong, 2011; Kang, 2013*

Overwegingen – van bewijs naar aanbeveling
De 90-dagen mortaliteit van een major hepatectomie was 7,4% in een meta-analyse voor iCCA en 9% in een meta-analyse voor pCCA (Van Keulen 2023; Franken 2019) De mortaliteit is nog hoger bij patiënten met een gecompromitteerd leverparenchym als gevolg van obstructie door galwegkanker, levercirrose, of na chemotherapie. Leverfalen is veruit de belangrijkste oorzaak van mortaliteit na partiele hepatectomie en ernstig leverfalen heeft een mortaliteit tot 50%. De grootte van de restlever is een sterke voorspeller van postoperatief leverfalen en mortaliteit. Het volume op CT van de restlever is de meest eenvoudige manier om de restfunctie te schatten. Experts hanteren een minimum volume van 30% voor een normale lever en 40% voor een gecompromitteerde lever.

Vena portae embolisatie (VPE) enkele weken voor de operatie van het deel van de lever dat bij de operatie wordt verwijderd heeft als doel om de restlever te laten groeien. Of VPE de kans op leverfalen en mortaliteit na resectie van iCCA of pCCA verkleint is niet onderzocht in gerandomiseerde trials. De enige twee vergelijkende studies die voldeden aan de inclusiecriteria waren klein (n=35 en 33). Deze studies waren ook nog retrospectief en daardoor onderhevig aan selectie bias. Mogelijk kregen juist die patiënten VPE met een kleinere restlever of gecompromitteerd leverparenchym. Deze patiënten hadden a priori al een verhoogde kans op leverfalen. De geëxcludeerde studies gingen over andere indicaties voor leverresecties of vergeleken niet een cohort met en zonder VPE. Het bewijs was onvoldoende om conclusies te trekken over de effectiviteit van VPE.

Bovendien includeerden beide studies alleen patiënten die daadwerkelijk een resectie hebben ondergaan. Hierdoor bleven patiënten ten onrechte buiten beschouwing, als ze door onvoldoende toename van de geplande restlever of complicaties van VPE geen operatie konden ondergaan. Een later verschenen studie beschreef dat er na VPE voor biliaire tumoren bij 133 patiënten (133/172, 77,3%) een chirurgische procedure is verricht

(Yamashita 2017). Een andere grote studie van 494 patiënten (Ebata 2012) was gëxcludeerd in het literatuuroverzicht omdat de uitkomsten van interesse niet waren gerapporteerd voor de vergelijking tussen de VPE versus non-VPE groepen. Deze studie vond dat 372 patiënten (75,3%) na VPE voor biliaire tumoren een partiele hepatectomie ondergingen. Bij 122 patiënten (24,7%) was géén hepatectomie verricht wegens peritoneale, lever, of lymfklier metastases, en/of een lokaal uitgebreide ziekte.

Slechts twee studies voldeden aan de vooraf gekozen inclusiecriteria. Enkele grote series die niet aan de inclusiecriteria voldeden geven ons echter enkele duidelijke handvatten voor het gebruik van PVE.

Voor pCCA geldt dat bij een rechtszijdige resectie leverfalen vaker lijkt voor te komen dan bij een linkszijdige, dit wordt verklaard door het verschil in volume tussen de rechter- en linkerzijde van de lever (Franken, 2021). Op functie en volumemeting gebaseerde VPE lijkt in de praktijk vooral rechtszijdige resecties te betreffen. Olthof (2020) beschrijft in een retrospectieve muti-institutionele, internationale cohortstudie van 1667 patiënten, na vergelijking middels propensity score matching, duidelijke voordelen voor VPE met betrekking tot post-operatief leverfalen (van 36% naar 8%), gallekkage (van 35% naar 10%), intra-abdominale abcessen (van 34% naar 19%) en een reductie van de 90-dagen mortaliteit van 18% naar 7%. In een studie van Huiskens (2018) werd in een retrospectieve analyse van bijna 800 patiënten reeds gesuggereerd dat er geen negatieve impact van VPE op lange termijn uitkomsten zijn na leverresectie voor oncologische aandoeningen. Dit is in lijn met de ervaring in een groot Nederlands centrum waar de mortaliteit drastisch daalde na het routinematig gebruik van VPE (Franken, 2020). Deze studies maken ook duidelijk dat het doen van een VPE naast een therapeutische tool ook een diagnostische en prognostische waarde heeft in demanagement van patiënten met perihilair cholangiocarcinoom. Uitblijven van hypertrofie is een indicator voor matig regeneratief potentieel. Er zijn een paar keerzijdes van het liberaal toepassen van PVE; Ten eerste worden bij patiënten die na VPE geen resectie ondergaan in het ziektebeloop meer leverabcessen gezien dan bij patiënten die geen VPE ondergingen (Huisman, 2017). Ten tweede betekent embolisatie van een kant van de lever dat er niet meer per-operatief van kant kan worden gewisseld. Dit is vooral bij pCCA soms een probleem omdat de uitbreiding van de tumor op beeldvorming dikwijls onbetrouwbaar te beoordelen is. Bij een wissel van linker resectie naar rechter resectie moet men er op beducht zijn dat de restlever kleiner zal zijn en wellicht eerst een PVE nodig is. Eerst PVE en resectie in tweede tempo lijkt dan een soms een betere optie. Verandering van strategie per operatief bleek in een Franse root-cause analyse een sterke indicator voor postoperatief leverfalen en mortaliteit (Khaoudy, 2018).

Over gebruik van PVE, maar ook andere methoden om de FLR te vergroten, is bij resecties voor andere indicaties dan galweg- of galblaaskanker is aanzienlijk meer gepubliceerd. In het review van Heil et al. worden de verschillende technieken in historische context beschreven. Associated liver partition and portal vein ligation (ALLPS) is een combinatie van transectie van het leverparenchym en onderbinden of emboliseren van de vena portae naar het deel van de lever met de tumor. De lever met de tumor wordt vervolgens pas verwijderd bij een tweede operatie circa 2 weken later. De initiële resultaten waren verbluffend en er is een aanzienlijk grotere hypertrofie respons na ALPPS in vergelijking met PVE. Voor colorectale levermetastasen is daarom een ALPPS procedure een gedegen alternatief gebleken als VPE niet voldoende lijkt. Met ook een oncologisch voordeel op lange termijn (Hasselgren, 2021). Voor patiënten met pCCA lijkt ALPPS te leiden tot minder goede resultaten. Er worden veel infectieuze complicaties gezien met beschreven een 90-dagen mortaliteit tot 48% (Olthof

2017). In geselecteerde gevallen kan het wel worden gebruikt als reddingsstrategie als een PVE onvoldoende heeft opgeleverd (Lang, 2020).

In meer recente literatuur wordt ook PVE met simultane deprivatie van een levervene beschreven (venous deprivation, DVE). DVE/PVE leidt tot een snellere en grotere hypertrofie respons dan PVE alleen. Het complicatie profiel lijkt meer op dat van PVE en is dus veel veiliger dan ALPPS. Voor patiënten die onvoldoende respons op PVE (zullen) hebben is een VPE met DVE een beter alternatief dan ALPPS. Er is een grote internationale studie opgezet om de waarde en vooral ook selectie van patiënten voor gecombineerde PVE/DVE te bepalen. (DRAGON Study)

Om onnodige complicaties, kosten en overbehandeling te voorkomen is het zinvol om juist die patiënten te selecteren die baat hebben bij een PVE. Hiervoor is schatting van de restleverfunctie nodig. De meest voor de hand liggende methode is schatting van het restlevervolume middels CT of MR- volumetrie. Volumetrie veronderstelt dat de leverfunctie homogeen is verdeeld over de lever. Bij gezonde patiënten met een normale lever is dit waarschijnlijk. Bij een onderliggende leverziekte kan volumetrie de restfunctie onderschatten of juist overschatten. Aanvullende tests van de totale leverfunctie kunnen de benodigde informatie opleveren. Algemene laboratoriumtesten en bijvoorbeeld een berekende ALBI-score zijn alleen van waarde bij patiënten met een ernstige onderliggende ziekte. De meeste patiënten met matige leverbeschadiging zullen normale laboratoriumbevindingen hebben. Andere tests zoals de ICG-klaringstest of de LIMAX-stofwisselingstest kunnen in deze gevallen aanvullende informatie bieden. Bij een door cholestase gecompromitteerde lever is vaak de functie ook nog eens ongelijkmatig en asymmetrisch verdeeld, de totale leverfunctie zegt dan weinig over de FLR-leverfunctie. Hepatobiliaire scintigrafie met ^{99m}TC gelabeld mebrofenine is een techniek die ruimtelijke verdeling, volume en totale functie combineert. Hepatobiliaire scintigrafie is klinisch gevalideerd en kan mogelijk beter postoperatief leverfalen voorspellen dan volume alleen (Olthof, 2023; Arntz, 2023). De absolute toegevoegde klinische waarde van deze technieken boven alleen volumetrie is echter nog onvoldoende bewezen.

Tot slot is duidelijk dat de geïntegreerde work-up van patiënten met pCCA waarbij drainage strategie (zie module ‘Preoperatieve galwegdrainage’) en lever augmentatie van de FRL nauw op elkaar af gestemd dienen te worden bij uitstek in een chirurgisch expertise centrum dient plaats te vinden.

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

Om voldoende restlever te verkrijgen lijkt een percutane VPE tot minder complicaties te leiden dan een onveiliger geachte ALPPS procedure, terwijl beiden tot een toename van de restlever leiden. Het lijkt aannemelijk dat hierdoor de patiënt voor een percutane VPE zou kiezen wanneer de restlever te klein blijkt. Ondanks dat er in case series weinig complicaties en mortaliteit worden geobserveerd die gerelateerd kunnen worden aan de VPE, is het wel een aanvullende ingreep die de patiënt ondergaat voorafgaand aan een resectie. Het kan in sommige gevallen blijken dat de percutane VPE niet zal leiden tot de mogelijkheid om een chirurgische resectie te doen. Het is daarom belangrijk om de aanwezige risico’s en eventuele gevolgen met de patiënt te bespreken en de voor- en nadelen gezamenlijk af te wegen.

Kosten (middelenbeslag)

Omdat de effectiviteit van VPE onduidelijk is, geldt dat ook voor de kosteneffectiviteit. Een VPE kost enkele duizenden euro’s. Echter, het middelenbeslag is beperkt omdat het aantal

patiënten met galwegkanker dat mogelijk in aanmerking komt voor een VPE slechts ongeveer 100 is per jaar. Daarbij komt dat de kosten van leverfalen en daarbij komende IC en langere afdelingsopname van één patiënt al voldoende zal zijn om alle PVE procedures in Nederland van dat jaar te bekostigen.

Aanvaardbaarheid, haalbaarheid en implementatie
De leverfunctie en het levervolume van de restlever kan onvoldoende blijken bij metingen. Volumetrie is breed beschikbaar en kan al worden uitgevoerd in de praktijk; het is haalbaar en er worden hier geen implementatieproblemen bij verwacht. Bij het uitvoeren van de VPE lijkt in prospectieve case series een laag aantal procedure-gerelateerde complicaties en zelden procedure-gerelateerde mortaliteit geobserveerd te worden. De aanbeveling is in overeenstemming met de huidige zorg in de praktijk.

Aanbevelingen
Aanbeveling-1
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Prospectieve case series en systematic reviews laten zien dat VPE bij patiënten met intrahepatisch en perihilair galwegcarcinoom leidt tot een laag aantal procedure gerelateerde complicaties en een hoge resection rate met een laag percentage postoperatief leverfalen. Er zijn geen goede vergelijkende studies waarin dit bevestigd wordt, maar zulke studies zijn niet uitvoerbaar omdat resectie bij patiënten met een te kleine FRL tot een onaanvaardbaar hoge mortaliteit ten gevolgde van postoperatief leverfalen zal leiden. De aanbeveling komt derhalve tot stand met bovenbeschreven best available evidence. Case series laten ook zien dat het aantal complicaties bij een percutane VPE lager is dan bij een ALPPS, terwijl beide technieken tot een significante toename van FLRb volume en functie leiden. Ook hier zijn geen goede directe vergelijkende studies beschikbaar

Verricht een percutane pre-operatieve vena portae embolisatie bij patiënten met galblaas of galwegkanker bij wie een leverresectie gepland wordt en het volume en/ of de functie van de future remant liver onvoldoende wordt geacht.

- Bij deze patiënten is het aannemelijk dat er onderliggend leverlijden is of galwegobstructie als etiologische factor. Daarom is het advies om een restvolume van minstens 40% aan te houden.

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Bijlagen bij hoofdstuk 8 Preoperatieve vena porta embolisatie

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

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Hong 2011	Type of study: Retrospective cohort Setting and country: Hospital, Korea Funding and conflicts of interest: Supported by the Korean ministry for health, welfare and family affairs through a grant of the Korea Healthcare technology R&D project. Authors declare that there is no conflict of interest.	Inclusion criteria: Patients had to undergo right extended hemihepatectomy, patients had hilar cholangiocellular carcinoma, patients underwent resection at the department of surgery in the Severance Hospital (Yonsei university collece of medicine, Korea). Exclusion criteria: Not described. N total at baseline: Intervention: 14 Control: 21 Important prognostic factors[2]: *Median age (range): I: 62 (49-76) C: 58 (37-72)*	Describe intervention (treatment/procedure/test): An interventional radiologist used a percutaneous transhepatic ipsilateral approach to access the right portal vein under ultrasound guidance to perform a portal vein embolization. Portography was used to assess the portal vein anatomy, whereafter the portal vein was embolized. Several embolic materials were used, such as gelatine sponge, thrombin, coil, or polidocanol. Patients received a CT-scan 2-4 weeks after embolization. Patients received a right liver resection for their hilar cholangiocellular carcinoma.	Describe control (treatment/procedure/test): Patients received a right liver resection for their hilar cholangiocellular carcinoma without preoperative portal vein embolization.	Length of follow-up: Unclear Loss-to-follow-up: Unclear, retrospective analysis Incomplete outcome data: None described.	Outcome measures and effect size (include 95%CI and p-value if available): Mortality (after liver resection), n/ntotal (%): I: 3/14 (21.4%) C: 2/21 (9.5%) Reasons: liver failure Complications of embolization (intervention group only), n: Fever: 8/14 Abdominal pain: 5/14 Nausea: n=1 Biloma: 2/14 Hypotension: 1/14	No correction of possible confounding was found.

		Sex: *I: 8M/6F* *C: 9M/12F* *T-stage:* *I: T1-2 n=10 / T3-4 n=4* *C: T1-2 n=9 / T3-4 n=12* *Tumor differentiation:* *I: well to moderate n=12 / poor to mucinous n = 2* *C: well to moderate n=17 / poor to mucinous n = 4* *Nodal involvement (n involvement):* *I: 7* *C: 11* Operative procedure: I: hemihepatectomy n=4 / trisectionectomy n= 10 C: hemihepatectomy n=4 / trisectionectomy n= 17 Tumor invasion: I: to fibromuscular layer n=9 / to subserosal layer or more n=5					

		C: to fibromuscular layer n=11 / to subserosal layer or more n=10 Preoperative biliairy drainage (n yes): I: 12 C: 15 Groups comparable at baseline? No					
Kang 2013	Type of study: Observational, database Setting and country: Hospital, Korea Funding and conflicts of interest: supported by a grant from Seoul National University Hospital.Potential CoI not reported by the authors/journal.	<u>Inclusion criteria</u>: Surgically treated for hilar cholangiocarcinoma between 2005 and 2010 at Seoul National University Hospital, hepatectomy (for hilar cholangiocarcinoma) as a surgical intervention, future liver remnant ≤30% <u>Exclusion criteria</u>: Left extended hepatectomy <u>N total at baseline</u>: Intervention: 11 Control: 22 <u>Important prognostic factors</u>[2]: *Age ± SD:* *I: 65.4 (10.3)* *C: 64.6 (4.4)*	Describe intervention (treatment/procedure/test): Right sided portal vein embolization was performed prior to surgery (mean 15.8 days, range: 13-20 days). Embolic materials used: gel foam, ethanolamine oleate, microcoils Right sided hepatectomy was performed after portal vein ombolization.	Describe control (treatment/procedure/test): Right sided hepatectomy without portal vein embolization	<u>Length of follow-up</u>: Unclear, database study <u>Loss-to-follow-up</u>: None reported. <u>Incomplete outcome data</u>: None reported for the outcomes of interest.	Outcome measures and effect size (include 95%CI and p-value if available): <u>Complications of embolization (intervention group only), n:</u> Fever (>38 degrees): 4 <u>Postoperative complications, intra-abdominal bleeding, n:</u> I: 4/11 C: 3/22 <u>Postoperative complications, post-operative bleeding, n:</u> I: 1/11 C: 2/22 <u>Postoperative complications, sepsis, n:</u> I: 2/11 C: 1/22 <u>Mortality (in-hospital), n:</u>	Unadjusted data

		Sex ratio: *I: 1.2M:1F* *C: 2.7M:1F* *Bismuth classification:* *I: type IV n=9 (81.8%), type IIIa n=2 (18.2%)* *C: Type IV n=4 (18.2%), Type IIIa n=18 (81.8%* *N received biliary drainage:* *I: 11 (100%)* *C: 18 (81.8%)* *Initial future liver remnant (%, SD):* *I: 20.8% (4.3)* *C: 22.4% (3.6)* *Type of hepatectomy:* *I: right trisectionectomy n=6 (54.5%), extended right hemihepatectomy n=5 (45.5%)* *C: right trisectionectomy n=2 (9.1%), extended right hemihepatectomy n=20 (90.9%)* Groups comparable at baseline? Probably not (Bismuth				I: 2/11 (reasons: n=1 liver failure, n=1myocardial infarction) C: not reported	

		classification, type of surgery)					

Notes:

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

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Hong 2011	Unlikely Reason: sampled from the same population	Unlikely Reason: The only loss to follow up in the relevant outcomes seem to be caused by death. No indications that follow-up substantially differed between study arms.	Unlikely (all-cause mortality) Reason: unlikely the outcomes of interest were differently measured between groups (or were specifically different for one of the groups) due to the designs (database) of the study.	Likely Reason: There does not seem to be any correction for possible confounding.
Kang 2013	Unlikely Reason: sampled from the same population	Unlikely Reason: The only loss to follow up in the relevant outcomes seem to be caused by death. No indications that follow-up substantially differed between study arms.	Unlikely (all-cause mortality) Reason: unlikely the outcomes of interest were differently measured between groups (or were specifically different for one of the groups) due to the designs (database) of the study. Likely (complications) Reason: There is probably a lack of blinding of the patient and healthcare provider (the latter possibly also being the outcome assessor).	Likely Reason: There does not seem to be any correction for possible confounding.

1. Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.

2. 2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.
3. Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has “soft” (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.

Implementatieplan bij module 8 Preoperatieve vena porta embolisatie

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Verricht een percutane pre-operatieve vena portae embolisatie bij patiënten met galblaas of galwegkanker bij wie een leverresectie gepland wordt en het volume en/ of de functie van de future remant liver onvoldoende wordt geacht. • Bij deze patiënten is het aannemelijk dat er onderliggend leverlijden is of galwegobstructie als etiologische factor. Daarom is het advies om een restvolume van minstens 40% aan te houden.	< 1 jaar	Geen tot gering	Bekendheid met richtlijn	Geen: expertise, middelen en infrastructuur reeds voorhanden	Publicatie richtlijn	Wetenschappelijke verenigingen	

Table of excluded studies (search strategy)

Author and year	Reason for exclusion
Higuchi 2014	Wrong comparison: PVE in PCCA vs other hepatic tumors; the PCCA-group only contained 71.4% patients with perihilar cholangiocarcinoma, while the rest were gallbladder or other hepatic tumors.
Wajswol 2018	Did not report the outcomes of interest, seems to have no comparison
Lang 2020	Narrative review
Vivarelli 2015	Wrong intervention: ligation (in ALPPS procedure) instead of embolization, seems to include only single-arm studies
Xiang 2019	Wrong intervention: ligation (in ALPPS procedure) instead of embolization, does not seem to have a comparison
Yamashita 2017	Wrong comparison: compares PVE in different populations

Table of excluded studies (Glantzounis, 2017)

Author and year	Reason for exclusion
Kawasaki 2003	No comparison about PVE vs no PVE
Kakizawa 2006	No comparison about PVE vs no PVE
Denecke 2011	Wrong comparison: PVE vs hepatic artery embolization
Ebata 2012	None of the outcomes of interest were compared on PVE vs non-PVE
Malinowski 2015	Wrong comparison: PVE vs PVE+plug/coil
Geisel 2014	Wrong comparison: PVE vs PVE+plug/coil
Regimbeau 2011	No comparison about PVE vs no PVE
Lee 2010	Wrong comparison: R0 vs R1 resection
Sano 2006	Wrong comparison: with vs without complications
Hwang 2015	No comparison about PVE vs no PVE

Literature search strategy

Systematic reviews search filter

Embase.com	481	471
Medline Ovid	251	76
Total	**732**	**547**

New references: 81

Embase.com

'biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR 'bile duct') NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ab,ti,kw AND [english]/lim AND [2012-2019]/py NOT 'conference abstract':it NOT ([animals]/lim NOT [humans]/lim) AND ('systematic review'/exp OR 'meta analysis'/exp OR (((systematic*) NEAR/3 (review)) OR meta-analy* OR metaanaly*):ab,ti,kw)

Medline Ovid

exp Gallbladder Neoplasms/ or exp biliary tract neoplasms/ or exp bile duct neoplasms/ or exp cholangiocarcinoma/ or exp klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile duct) ADJ6 (carcinom* OR cancer* OR tumor* OR

tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ab,ti,kf. AND english.la. AND (2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020) NOT (exp animals/ NOT humans/) AND (Systematic Review/ OR Meta-Analysis/ OR (((systematic*) ADJ3 (review)) OR meta-analy* OR metaanaly*).ab,ti,kf.)

Trials search filter

Database searched	via	Years of coverage	Records	Records after duplicates removed
Embase	Embase.com	1971 - Present	767	760
Medline ALL	Ovid	1946 - Present	422	80
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	643	464
Total			**1832**	**1304**

Embase 766

('biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin*):ti,kw) AND [english]/lim AND [2015-2030]/py NOT 'conference abstract':it NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) AND (('clinical trial'/exp OR (trial):ab,ti,kw) OR [clinical trial number]/lim)

Medline Ovid 422

(exp *Gallbladder Neoplasms/ or exp *biliary tract neoplasms/ or exp *bile duct neoplasms/ or exp *cholangiocarcinoma/ or exp *klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ti,kf.) AND english.la. AND 2015:2030.(sa_year). NOT (exp animals/ NOT humans/) AND ((Clinical Trial/ OR (trial).ab,ti,kf.) OR clinicaltrials.si.)

Cochrane (2015-2020) 643

((((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ti)

Module 9 Indicatie resectie

Uitgangsvraag
Voor welke patiënten met een galweg- of galblaascarcinoom wordt chirurgische resectie geadviseerd?

Inleiding
De indicatie voor resectie van galweg- of galblaascarcinoom is een afweging tussen de voor- en nadelen van de resectie. Tegenover een mogelijke verbetering in overleving na resectie staan postoperatieve mortaliteit en complicaties met soms een langdurig herstel. Na resectie van een galweg- of galblaascarcinoom is de 5-jaars overleving in Nederland ongeveer 20% (Strijker, 2019; De Savornin Lohman, 2020). De 90-dagen mortaliteit voor pCCA was 9% en voor iCCA 7% in twee grote meta-analyses (Franken, 2019; Van Keulen, 2023).

Bij gemetastaseerde ziekte (stadium IV) is er zelden een indicatie voor resectie. Bij patiënten zonder metastasen is een resectie meestal chirurgisch-technisch mogelijk, maar niet altijd verstandig. Vooral bij patiënten met lokaal uitgebreide ziekte is het operatierisico groter en de mogelijke overlevingswinst kleiner. De overleving is voor die patiënten mogelijk even goed met palliatieve chemotherapie. Helaas is er geen consensus wanneer galweg- of galblaaskanker lokaal uitgebreid is.

Search and select
A systematic review of the literature was performed to answer the following question:
What are the (un)beneficial effects of a surgical resection on overall survival, 90-day post-operative mortality, and quality of life in patients with a locally advanced gallbladder cancer or cholangiocarcinoma when compared to systemic chemotherapy or best supportive care?

P: Patients with a locally advanced cholangiocarcinoma or gallbladder cancer
I: Surgical resection (e.g., liver resection, cholecystectomy, lymph node resection, pancreaticoduodenectomy)
C: Systemic chemotherapy or best supportive care
O: Overall survival, 90-day postoperative mortality, quality of life (including fear, fatigue, pruritus, depression, and physical condition)

<u>Relevant outcome measures</u>
The guideline development group considered overall survival as a critical outcome measure for decision making; and 90-day postoperative mortality and quality of life as important outcome measures for decision making.

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

The working group defined HR < 0.9 and HR > 1.11 as minimal clinically (patient) relevant differences for overall survival.

<u>Search and select (Methods)</u>
The databases Medline (via OVID) and Embase (via Embase.com) were searched for systematic reviews with relevant search terms until 31-08-2021. Medline (via OVID) and Embase (via Embase.com) were also searched until 12-01-2021 for trials with relevant search

terms. The detailed search strategy is depicted under the tab Methods. The systematic literature searches resulted in 1861 hits.

A preselection of potentially relevant literature for sections of the guideline was made by the guideline methodologists supporting the working group, excluding all obvious non-relevant articles for this section. When in slightest doubt the literature remained in the preselection for the current section. This resulted in the preselection of 523 hits from the total of 1861 hits. Thereafter, 52 studies were initially selected based on title and abstract screening by members of the working group. Studies were eligible for inclusion based on the following criteria: Patients had locally advanced gallbladder cancer or cholangiocarcinoma, a surgical resection was compared to systemic chemotherapy or best supportive care, one of the outcomes of interest was reported, and the study design was comparative with appropriate correction for plausible confounding (if relevant). Conference abstracts, poster abstracts, study protocols and narrative reviews were excluded. After reading the full text, 51 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 1 study was included.

Results

One study was included in the analysis of the literature (Moustafa, 2019). The important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Intrahepatic cholangiocarcinoma

Moustafa (2019) performed a retrospective comparative cohort study based on data from the SEER database to compare the effects of liver resection to palliative chemotherapy. Adult patients in the database were eligible when diagnosed with a locally advanced primary intrahepatic cholagiocarcinoma (stage III and IVa, AJCC 7th ed.), and had undergone a liver resection or had received palliative chemotherapy. Patients were excluded when they had a mixed intrahepatic cholangiocarcinoma and hepatocellular carcinoma, had unknown staging (Tx, Nx), had early disease (stage I or II according to either the 7th or 8th ed. of the AJCC), had distant metastases (stage IVb [AJCC 7th ed.] or stage IV [AJCC 8th ed.]), underwent a liver transplantation or local ablation or bile duct excision, or did not receive surgery and records did not indicate palliative chemotherapy was administered. Eligible participants were stratified into two different datasets according to the AJCC edition (7th or 8th ed.) used. For the AJCC 7th ed. dataset 315 patients were selected (n=154 received liver resection, n=161 received palliative chemotherapy), however 84 couples were propensity score matched. In the AJCC 8th ed. dataset, 233 patients were selected (n=100 received liver resection, n=133 received palliative chemotherapy) and 62 couples could be propensity score matched. Characteristics of the propensity score matched samples were not described.

Gallbladder cancer

No studies could be included from the literature search that matched the inclusion criteria for patients with gallbladder cancer.

Results

Intrahepatic cholangiocarcinoma

Overall survival

Moustafa (2019) furthermore reported several parameters and time-points of overall survival in complete case propensity matched samples, depending on the diagnosis following either the 7th or the 8th edition of the AJCC. Table 1 provides an overview of results

Table 1 – Overview of results on several parameters and time-points of overall survival using a complete case propensity matched sample, as reported in Moustafa (2019).

	Propensity score matched sample, AJCC 7th ed. (complete case)			**Propensity score matched sample, AJCC 8th ed. (complete case)**		
	Liver resection (n=154)	***Palliative chemotherapy (n=161)***	***Note***	***Liver resection (n=100)***	***Palliative chemotherapy (n=133)***	***Note***
Overall survival, multivariable analysis	Therapy (reference group = palliative chemotherapy): HR = 0.57 (95%CI: 0.35-0.93)		Other variables in the model: age, N1, multiple lesions, vascular invasion	-		-
Median overall survival	35 months (95%CI: 2.5-57.5)	14 months (95%CI: 9.1-18.8)	Log-rank test: p=0.007	17 months (95%CI: 8.1-25.8)	12 months (95%CI: 8.7-15.2)	Log-rank test p=0.013
One-year survival rate	64.3%	51.6%	-	57.8%	54.3%	-
Two-year survival rate	51.1%	16.4%	-	43.4%	7.4%	-
Three-year survival rate	40.8%	5.5%	-	32.6%	3.7%	-

Moustafa (2019) also reported some of the parameters in multiple imputed datasets, depending on the diagnosis following either the 7th or the 8th edition of the AJCC. Table 2 provides an overview of results.

Table 2 – Overview of results on several parameters and time-points of overall survival using propensity matched samples with multiple imputation for missing data, as reported in Moustafa (2019).

	Propensity score matched sample, AJCC 7th ed. (multiple imputed)			**Propensity score matched sample, AJCC 8th ed. (multiple imputed)**		
	Liver resection	***Palliative chemotherapy***	***Note***	***Liver resection***	***Palliative chemotherapy***	***Note***
Median overall survival	18 months (95%CI: 12.3-23.7)	14 months (9.9-18.1)	-	17 months (95%CI: 12.5-21.5)	10 months (95%CI: 8.5-11.5%)	-
1-year survival rate	66.5%	55.5%	-	61.2%	41.8%	-
2-year survival rate	43.7%	10.0%	-	37.7%	12.6%	-
3-year survival rate	30.6%	6.6%	Log-rank test: p=0.003	28.3%	4.2%	Log-rank test: p=0.008

90-day postoperative mortality

No studies included from the literature search reported the 90-day postoperative mortality for patients with a cholangiocarcinoma.

Quality of life
No studies could be included from the literature search that reported the quality of life for patients with a cholangiocarcinoma (including fear, fatigue, pruritus, depression, and physical condition).

Gallbladder cancer
No studies could be included from the literature search that matched the inclusion criteria for patients with a gall bladder carcinoma.

Level of evidence of the literature
Intrahepatic cholangiocarcinoma
GRADE starts on 'LOW' for observational studies. The level of evidence regarding the outcome measure overall survival was downgraded by 1 level because of the number of included patients (1 level for imprecision: small sample after propensity matching, the confidence interval of the HR in the multivariable analysis showing the association for resection [yes/no] crosses the border of clinical decision making); publication bias and inconsistency could not be assessed (reason: only 1 included study).

Assessing the level of evidence regarding the outcome measures 90-day postoperative mortality and quality of life in patients with a cholangiocarcinoma was not performed because no studies were found that matched the inclusion criteria.

Gallbladder cancer
Assessing the level of evidence regarding the outcome measures in patients with a gallbladder cancer was not performed because no studies were found that matched the inclusion criteria.

Conclusions
Intrahepatic cholangiocarcinoma

VERY LOW GRADE	We are unsure about the effects of resection compared to systemic chemotherapy on the overall survival in patients with a locally advanced intrahepatic cholangiocarcinoma. No studies were found that reported the effects on overall survival when comparing resection to best supportive care for patients with a locally advanced intrahepatic cholangiocarcinoma. No studies were found that reported the effects on overall survival when comparing resection to systemic chemotherapy or best supportive care for patients with other locally advanced cholangiocarcinomas. *Sources: Moustafa, 2019*

NO GRADE	No studies were found that reported 90-day postoperative mortality or quality of life when comparing resection to systemic chemotherapy or best supportive care for patients with a locally advanced cholangiocarcinoma.

Perihilar cholangiocarcinoma

NO GRADE	No studies were found that matched the selection criteria for patients with a locally advanced perihilar cholangiocarcinoma.

Gallbladder cancer

NO GRADE	No studies were found that matched the selection criteria for patients with a locally advanced gallbladder cancer.

Overwegingen – van bewijs naar aanbeveling

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

De 90-dagen mortaliteit voor perihilair cholangiocarcinoom (pCCA) was 9% en voor intrahepatisch cholangiocarcinoom (iCCA) 7% in twee grote meta-analyses (Franken, 2019; Van Keulen, 2023). Ernstige postoperatieve complicaties na leverchirurgie treden op in ruim 20% van de patiënten met iCCA en galblaascarcinoom (GBC) en ruim 40% met pCCA (van Keulen 2023, Franken 2019, Kuipers 2020). Deze complicaties zijn vaak het gevolg van leverfalen, gallekkage of sepsis. De optimale korte termijn chirurgisch uitkomst – de textbook outcome – is gedefinieerd als een beloop zonder ernstige complicaties, verlengde opname duur of heropname. In een studie van een expert centrum in Duitsland werd de textbook outcome in slechts 24% van de patiënten behaald (Benzing, 2022).

De lange termijn overleving na resectie is afhankelijk van de kans op een radicale (R0) resectie (Rassam, 2018). De kans hierop is kleiner bij een lokaal uitgebreid galweg- of galblaaskanker. Consensus ontbreekt over wanneer een galweg- of galblaaskanker lokaal uitgebreid is. Ook in de recente Internationale richtlijnen van de ESMO (Vogel, 2023) en de NCCN (NCCN, 2023) ontbreken eenduidige definities van lokaal gevorderd galweg- en galblaaskanker. Bij de meeste definities gaat het om betrokkenheid van of ingroei in omliggende organen (b.v., het colon bij galblaaskanker) of structuren (b.v., de arteria hepatica bij pCCA). Maar ook de aanwezigheid van lymfkliermetastasen of van multifocale ziekte bij iCCA wordt vaak als lokaal uitgebreide ziekte geduid. Ongeacht het gebrek aan eenduidige definitie van lokaal-uitgebreid galweg- en galblaaskanker, moet een multidisciplinair team van experts samen met de patiënt de kans op complicaties van de operatie afwegen tegen een mogelijk voordeel in lang termijn overleving (Van Keulen, 2023).

Ervaring met complexe leverchirurgie is voorspellend voor betere uitkomsten voor patiënten met galweg- en galblaaskanker (Mueller, 2022). Verwijzing naar een centrum met expertise is daarom belangrijk, zowel voor patiënten die mogelijk in aanmerking komen voor een resectie als voor patiënten die niet in aanmerking komen voor een resectie. De kans om een resectie te ondergaan was bovendien hoger voor patiënten die zich bij diagnose presenteerden in een academisch ziekenhuis in vergelijking met een niet-academisch ziekenhuis (Van Keulen, 2021). Dit verschil resulteerde ook in een betere overleving.

Voor alle patiënten met galweg- en galblaaskanker geldt dat een resectie (zelden) zinvol is als er sprake is van metastasen (stadium IV). Hieronder vallen ook positieve extraregionale lymfklieren waaronder die bij de truncus coeliacus en in het aortocavale window.

Voor alle patiënten met galweg- en galblaaskanker geldt eveneens dat een chirurgische resectie alleen zinvol is als er een R0 resectie mogelijk is mét behoud van voldoende restlevervolume (>40%, bij een normale restlever). Als de restlever kleiner is dan 40%, kan een vena portae embolisatie (VPE) leiden tot voldoende hypertrofie (zie Module 'VPE embolisatie').

De kans op het vinden van occulte metastasen ondanks adequate preoperatieve beeldvorming bij patiënten met galweg- of galblaascarcinoom varieert van 10% tot 25%. Deze hoge kans rechtvaardigt een diagnostische laparoscopie in alle patiënten voorafgaand aan een laparotomie. De kans op palliatieve chemotherapie bij de diagnose van occulte metastasen is kleiner na een laparotomie dan alleen een diagnostische laparoscopie.

Intrahepatisch cholangiocarcinoom

In de literatuurstudie voor de PICO is slechts één vergelijkend cohort (Moustafa, 2019) gevonden die chirurgische resectie met systemische therapie vergeleek bij patiënten met een lokaal uitgebreid intrahepatisch cholangiocarcinoom en corrigeerde voor plausibele confounders. Moustafa (2019) gebruikte hiervoor de SEER-database en analyseerde afzonderlijk patiënten die volgens de TNM 7^{e} editie (stadium III en IVa) en TNM 8^{e} editie (stadium III) waren gestadiëerd. Voor beide edities betrof het patiënten met betrokkenheid van het viscerale peritoneum, ingroei in structuren buiten de lever, of positieve lymfklieren. In een propensity score gekoppelde analyse van de TNM 7^{e} editie-groep, was resectie geassocieerd met een betere overleving (HR = 0,6, 95% BHI: 0,4-0,9). In de propensity score was rekening gehouden met leeftijd, lymfklier-status, meerdere laesies en vasculaire invasie. De 3-jaars overleving was ook beter voor de resectie-groep; 40,8% vs. 5,5% (TNM7, log-rank: p=0,007). De resultaten voor TNM8 waren vergelijkbaar met die voor TNM7. Enerzijds is dit verschil indrukwekkend groot, anderzijds is er ondanks propensity score matching mogelijk nog sprake van confounding by indication, omdat niet voor alle confounders is gecorrigeerd.

In zowel de 7^{e} als 8^{e} editie van de TNM classificatie is er bij de aanwezigheid van multipele tumoren in de lever slechts sprake van T2 en stadium II. Een grote internationale studie heeft laten zien dat de mediane overleving van deze patiënten slechts 18 maanden was, zodat het beter is hen als stadium IV te beschouwen (Lamarca, 2021). Ook bij patiënten met iCCA en positieve lymfklieren was de mediane overleving na resectie slechts 20 maanden, vergeleken met 60 maanden bij negatieve lymfklieren (Jolissaint, 2021). Deze mediane overleving is vergelijkbaar met de mediane overleving van 17 maanden met palliatieve chemotherapie met gemcitabine plus cisplatin voor lokaal uitgebreid iCCA (Lamarca, 2020 en Module 11). Anderzijds is de 3-jaars overleving wel beter na resectie bij positieve klieren (25%) of multifocale ziekte (30%) vergeleken met palliatieve chemotherapie (3%) (Jolissaint, 2021; Franssen, 2022; Lamarca, 2020). De werkgroep adviseert om bij patiënten met multifocaal iCCA of bij iCCA met positieve lymfklieren niet standaard een resectie te doen.

Perihilair cholangiocarcinoom

De literatuurstudie heeft geen studies gevonden die uitkomsten vergeleken tussen patiënten met pCCA die een resectie of palliatieve chemotherapie ondergingen. De kans op een radicale resectie hangt mede af van de uitgebreidheid van galwegcarcinoom in de galwegen en de betrokkenheid van bloedvaten. De Bismuth classificatie beschrijft de uitgebreidheid van pCCA in de galwegen. Bismuth IV betekent betrokkenheid van de sectorale (2^{e} orde) galwegen zowel links als rechts. Dit maakt de kans op een radicale resectie kleiner. In het verleden werd Bismuth IV beschouwd als een contra-indicatie voor resectie, echter een grote Japanse studie vond dat voor patiënten met Bismuth IV en negatieve lymfklieren de 5-jaars overleving ruim 50% was (Ebata 2018). Als het

galwegcarcinoom zowel de vena portae als in de arteria hepatica van de toekomstige restlever infiltreert, is een resectie zelden zinvol. Vaak is op beeldvorming preoperatief niet met zekerheid te zeggen of contact van de tumor met deze bloedvaten ook daadwerkelijk infiltratie in de vaatwand betreft. Vaak is een chirurgische exploratie nodig om te beoordelen of een R0 resectie mogelijk is. Echter, als het vaatcontact op beeldvorming meer dan 180 graden betreft, is vaatingroei wel waarschijnlijker (Franken, 2021). De mediane overleving bij patiënten met contact van de tumor met de linker of rechter arteria hepatica van tenminste 180 graden (ongeacht of zij een resectie ondergingen) was minder dan 1 jaar (Van Vugt, 2018). Patiënten met positieve lymfklieren hadden een mediane overleving na resectie van 19 maanden en een 3-jaars overleving van 27% (Buettner, 2017). De werkgroep adviseert om bij patiënten met meer dan 180 graden vaatcontact met de arteria hepatica van de toekomstige restlever, evenals bij patiënten met positieve lymfklieren niet standaard een resectie te doen. Patiënten met lokaal uitgebreid pCCA, maar met negatieve lymf klieren, komen onder strikte criteria in aanmerking voor het landelijk protocol "levertransplantatie voor perihilair cholangiocarcinoom" (Breuer, 2022; Hoogwater, 2023). Het gaat hierbij overigens jaarlijks slechts om twee tot vier patiënten in Nederland.

Initieel was galwegcarcinoom een absolute contra-indicatie voor levertranplantatie. Echter, bij geselecteerde groepen patienten, na zeer intensieve behandeling met chemoradiotherapie, zijn er 5-jaars overlevingspercentages tot 73% gerapporteerd (Darwish Murad, 2012). Andere studies, met eveneens strenge selectiecriteria maar zonder intensieve neo-adjuvante behandeling, hebben 5-jaarsoverleving tot 58% laten zien (Friman, 2011). Deze resultaten hebben in Nederland geleid tot de ontwikkeling van het landelijk protocol. Recent zijn de eerste langetermijn resultaten van het landelijk protocol gepubliceerd (Hoogwater 2023).
De belangrijkste selectiecriteria zijn:
- Chirurgische resectie van het galwegcarcinoom is anatomisch of functioneel niet mogelijk;
- Geen eerdere percutane tumorbiopsie en/of chirurgische exploratie van de galwegen waarbij contact is geweest met het tumorgebied;
- Geen tumor groter dan 3cm, loodrecht gemeten op de galweg, zichtbaar op CT of MRI en geen aanwijzingen voor doorgroei in de pancreaskop;
- Geen aanwijzingen voor peritoneaal-, lymfeklier- en/of andere metastase.

<u>Galblaaskanker</u>
De literatuurstudie heeft ook geen studies gevonden die uitkomsten vergeleken tussen patiënten met GBC die een resectie of palliatieve chemotherapie ondergingen. Galblaaskanker kan als lokaal uitgebreid worden beschouwd bij ingroei in omliggende organen (b.v., colon, duodenum, of extrahepatische galweg), of bij positieve lymfklieren. De mediane overleving van patiënten met een galblaascarcinoom met locoregionale metastasen is circa 30 maanden na resectie (De Savornin Lohman, 2023; Zhang, 2018). In een studie van 81 patiënten met GBC die zich presenteerden met stille icterus (t.g.v. ingroei in de extrahepatische galweg) was de kans op ziekte-vrije overleving na 2-jaar 0% (Hawkins, 2004). De werkgroep adviseert om bij patiënten met GBC en een stille icterus geen resectie te verrichten. Bij patienten met ingroei in omliggende organen of positieve lymfklieren advsieert de werkgroep om niet standaard een resectie te verrichten.

<u>Galblaaspoliepen</u>
De internationale literatuur is niet eenduidig over de indicatiestelling voor een cholecystectomie bij incidenteel gevonden galblaaspoliepen. Dit gebrek aan consensus komt onder andere door de grote variatie in incidentie van het galblaascarcinoom wereldwijd. In

een westerse populatie wordt een cholecystectomie geadviseerd bij patiënten met een galblaaspoliep >10 millimeter, poliepen die meer dan 3 millimeter per jaar groeien en in patiënten met primaire scleroserende cholangitis (PSC). In Nederlandse patiënten zonder familiair risico op biliaire tumoren of PSC is het risico op het ontwikkelen van galblaaskanker zeer klein. Bij poliepen kleiner dan 5 millimeter is er geen indicatie voor follow-up. Bij poliepen tussen 6-9 millimeter wordt follow-up geadviseerd voor twee jaar (controle na 6 maanden, 1 jaar en 2 jaar). Indien er geen groei plaats vindt mag follow-up worden gestaakt. Indien er een echografisch beeld is van adenomyomatosis (wandverdikking met microcystes (Rokitansky-Arschoff sinussen) of comet-trail artefacts) is er geen indicatie voor cholecystectomie of follow-up, ook niet bij een afwijking groter dan 1 centimeter (Kamaya, 2022; Foley, 2022; Wennmacker, 2019; Pang, 2018; Golse, 2017).

Inductie chemotherapie

Lokaal gevorderd galweg- of galblaaskanker is een systemische ziekte; 10 jaar na de operatie is de overleving vrijwel nihil. Inductie chemotherapie (al of niet gevolgd door radiotherapie) is onderzocht in retrospectieve studies (Dhote, 2023; Choi 2023). Het biedt de mogelijkheid om alleen patiënten met een goede respons te selecteren voor resectie. Dit voorkomt mogelijk een risicovolle resectie bij patiënten die geen levensverlenging door der operatie krijgen omdat ze binnen een jaar na operatie al metastasen hebben. Prospectieve studies moeten onderzoeken of inductie chemotherapie daadwerkelijk levensverlengend is.

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

Het is belangrijk om de waarde van een radicale resectie te bespreken met de patiënt als er een mogelijkheid tot resectie is. Er bestaat een grote kans op (ernstige) postoperatieve morbiditeit. Hierbij is bijvoorbeeld te denken aan gallekkage en leverfalen, re-operaties en heropnamen (Mueller 2022). Het is aannemelijk dat deze (ernstige) complicaties kunnen leiden tot een verminderde kwaliteit van leven van de patiënt. Indien een radicale resectie niet (meer) mogelijk is, is het belangrijk om de gevolgen van systemische therapie te bespreken met de patiënt. Door de aard van deze interventie zal het patroon van morbiditeit verschillen met die van een resectie. Denk hierbij bijvoorbeeld aan (ernstige) hand-voet syndroom, vermoeidheid, diarree, buikpijn en/ of misselijkheid bij capecitabine (Primrose, 2019). Zie hiervoor ook de modules over systemische behandeling (‘Adjuvant’, ‘eerstelijns inductie/palliatief’ en ‘tweedelijns en derdelijns’).

Aanvaardbaarheid, haalbaarheid en implementatie

De in deze module besproken chirurgische resecties worden al uitgevoerd in de praktijk, waardoor er op dit vlak geen implementatieproblemen van de aanbevelingen worden verwacht. De aanbevelingen zijn daarmee in overeenstemming met de huidige zorg.

Aanbevelingen

Aanbeveling-1

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

Preoperatieve diagnostiek en patiënt-optimalisatie zijn belangrijk. Het lijkt erop dat ervaring en expertise correleert met gunstige uitkomsten. Verwijzing naar een centrum met expertise is daarom belangrijk, zowel voor patiënten die mogelijk in aanmerking komen voor een resectie als voor patiënten die niet in aanmerking komen voor een resectie.

Verricht de beoordeling voor resectie van een galweg- of galblaascarcinoom in een centrum met chirurgische expertise van het galweg- en galblaascarcinoom.

Aanbeveling-2
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Er is geen bewijs om een resectie van het galweg- of galblaascarcinoom uit te voeren bij aanwezigheid van metastasen op afstand.

Verricht geen resectie van het galweg- of galblaascarcinoom bij patiënten met metastasen (stadium IV). Hieronder vallen ook positieve extraregionale lymfklieren waaronder die bij de truncus coeliacus en in het aortocavale window.

Aanbeveling-3
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Er wordt geadviseerd om bij patiënten met een galwegcarcinoom een chirurgische resectie alleen dan te doen wanneer een R0 resectie kan worden verkregen met behoud van voldoende restlevervolume (>40%) en met inachtneming van de lokale anatomie van de galwegen in de leverhilus.

Laat iedere patiënt met een galweg- of galblaascarcinoom in aanmerking komen voor resectie wanneer een complete (R0) resectie mogelijk lijkt.

Aanbeveling-4
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
De kans op het vinden van occulte metastasen ondanks adequate preoperatieve beeldvorming bij patiënten met galweg- of galblaascarcinoom varieert van 10% tot 25%. De kans op palliatieve chemotherapie bij de diagnose van occulte metastasen is kleiner na een laparotomie dan alleen een diagnostische laparoscopie.

Verricht een diagnostische laparoscopie voorafgaand aan een laparotomie bij alle patiënten met galweg- of galblaascarcinoom.

Aanbeveling-5
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Patiënten met iCCA en multifocale ziekte in de lever of positieve lymfklieren hebben een mediane overleving na resectie die vergelijkbaar is met palliatieve chemotherapie. De 3-jaars overleving is wel beter na resectie en moet worden afgewogen tegen het risico van de operatie.

Verricht niet standaard een resectie bij patiënten met intrahepatisch cholangiocarcinoom en multifocale ziekte in de lever of positieve lymfklieren.

Aanbeveling-6
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie

Patiënten met pCCA en betrokkenheid van meer dan 180 graden van de arteria hepatica naar de toekomstige restlever of met positieve lymfklieren hebben een slechte mediane overleving. De 3-jaars overleving is wel beter na resectie vergeleken met systemische chemotherapie en moet worden afgewogen tegen het risico van de operatie.

Verricht niet standaard een resectie bij patiënten met perihilair cholangiocarcinoom en meer dan 180 graden betrokkenheid van de arteria hepatica naar de toekomstige restlever of positieve lymfklieren.

Aanbeveling-7
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Patiënten met galblaaskanker en bij presentatie een stille icterus hebben een zeer beperkte overleving. Na resectie is de mediane overleving van patienten met een stille icterus 7,7 maanden (2-jaarsoverleving 17%) versus 26,1 maanden bij patiënten zonder icterus (2-jaarsoverleving 39%) (de Savornin Lohman, 2020). De overleving na resectie bij positieve klieren is minder slecht.

Verricht niet standaard een resectie bij patiënten met galblaaskanker en een stille icterus bij presentatie of bij patiënten met positieve lymfklieren.

Aanbeveling-8
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Galblaaspoliepen worden meestal incidenteel vastgesteld vanwege een toename aan beeldvormende diagnostiek. De kans dat een poliep maligne ontaard in een westerse populatie is zeer gering. Aanbeveling 8 is in lijn met de Europese richtlijn (Management and follow-up of gallbladder polyps: updated joint guidelines between the ESGAR, EAES, EFISDS and ESGE – Foley, 2022)).

Voer geen cholecystectomie en follow-up uit bij patiënten met een galblaaspoliep ≤ 5 millimeter. Verricht een één- tot maximaal twee-jarige echografische follow-up bij patiënten met een galblaaspoliep tussen 6-10 millimeter. Verricht een cholecystectomie bij patiënten met een galblaaspoliep >10 millimeter, poliepen die meer dan 3 millimeter per jaar groeien en in patiënten met primaire scleroserende cholangitis (PSC). Verricht geen cholecystectomie indien er een echografisch beeld is van adenomyomatosis, ook niet bij afwijkingen >1 centimeter.

Aanbeveling-9
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventie
Patiënten met lokaal uitgebreid galweg- of galblaaskanker komen in aanmerking voor palliatieve systemische therapie (Module 11), als ze niet in aanmerking komen voor een

operatie. In geselecteerde patienten kan bij restadiëring na systemische behandeling een resectie worden heroverwogen.

Heroverweeg een resectie bij patiënten met een lokaal gevorderd galweg- of galblaascarcinoom en een goede response op systemische chemotherapie.

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Bijlagen bij module 9 Indicatie resectie

Evidence tables

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

This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Moustafa 2019	Type of study: Retrospective database (comparative cohort) Setting and country: SEER hospital data (US) Funding and conflicts of interest: Authors declare that there are no CoI's and no funding sources.	Inclusion criteria: Adult patients, diagnosed with locally advanced primary intrahepatic cholangiocarcinoma (stage III and IVa, AJCC 7th ed.), had undergone liver resection or palliative chemotherapy. Exclusion criteria: Mixed intrahepatic cholangiocarcinoma and hepatocellular carcinoma, unknown staging (Tx, Nx), early disease (stage I, II according to either AJCC 7th or 8th ed.), distant metastases (stage IVb in the AJCC 7th e.d. or stage IV in the 8th ed.), received	Describe intervention (treatment/procedure/test): Liver resection (procedures not further described)	Describe control (treatment/procedure/test): Palliative chemotherapy (procedures not further described)	Length of follow-up: 3 years (for overall survival) Loss-to-follow-up: NA (retrospective database, complete case and imputed datasets) Incomplete outcome data: *AJCC 7th ed. / complete case set (84 matches):* Intervention: 70 (70/154, 45.5%) Control: 77 (77/161, 47.8%) *AJCC8th ed. /complete case set (62 matches):* Intervention: 38 (38/100, 38%) Control: 71 (71/133, 53,4%)	Outcome measures and effect size (include 95%CI and p-value if available): Propensity-matched 3-year median overall survival (ACJJ 7th ed. complete case set): I: 35 months (95%CI: 2.5-57.4) C: 14 months (95%CI: 9.1-18.8) Propensity-matched 1-year overall survival rate (ACJJ 7th ed. complete case set): I: 64.3% C: 51.6% Propensity-matched 2-year overall survival rate (ACJJ 7th ed. complete case set): I: 51.1% C: 16.4%	Cases with incomplete data were excluded in the complete case analyses -> propensity matching was performed only in complete cases: - ACCC 7th ed. set had 84 matches - AJCC 8th ed. set had 62 matches SEER database does not differentiate between satellitosis, multifocal tumors, and intrahepatic metastases, and refers to them as "multiple (satellite) nodules/tumors". Propensity score was calculated by a logistic regression, using: age, race, T, lymph node status, multifocality, vascular

		liver transplantation / local ablation / bile duct excision, did not receive surgery and records did not indicate palliative chemotherapy was provided. <u>N total at baseline</u>: ACCJ 7th ed./complete case set Intervention: 154 Control: 161 AJCC 8th ed. Set Intervention: 100 Control: 133 <u>Important prognostic factors (ACCJ 7th ed./complete case set)[2] :</u> *age ≥65:* *I: 85 (55%)* *C: 71 (44%)* *Sex:* *I: 51% M* *C: 49% M* *Race:* I: white 81%/ black 6% / other 13% C: white 76%/ black 14% / other 9% *Stage:* I: stage III 19% / stage IVa 81%				Propensity-matched 3-year overall survival rate (ACJJ 7th ed. complete case set): I: 40.8% C: 5.5% Log-rank test: p=0.007 -- Propensity-matched 3-year median overall survival (ACJJ 8th ed. complete case set): I: 17 months (95%CI: 8.1-25.8) C: 12 months (95%CI: 8.7-15.2) Propensity-matched 1-year overall survival rate (ACJJ 8th ed. complete case set): I: 57.8% C: 54.3% Propensity-matched 2-year overall survival rate (ACJJ 8th ed. complete case set): I: 43.4% C: 7.4% Propensity-matched 3-year overall survival rate (ACJJ 8th ed. complete case set): I: 32.6% C: 3.7% Log-rank test: p=0.013 -- Propensity-matched 3-year median overall survival (AJCC 7th ed. multiple imputation set):	invasion, and cause of death (as registered in SEER).

		C: stage III 19% / stage IVa 81% T status: I: T1 14% / T2 27% / T3 27% / T4 32% C: T1 17% / T2 36% / T3 29% / T4 19% N status: I: N0 43% / N1 57% C: N0 29% / N1 71% Groups comparable at baseline? Unclear, characteristics of propensity-matched samples in analyses not described. Not comparable for direct comparison (without propensity matching), e.g. see N-stage, multifocality, and histological grade.				I: 18 months (95%CI: 12.3-23.7) C: 14 months (95%CI: 9.9-18.1) Propensity-matched 1-year overall survival rate (AJCC 7th ed. multiple imputation set): I: 66.5% C: 55.5% Propensity-matched 2-year overall survival rate (AJCC 7th ed. multiple imputation set): I: 43.7% C: 10.0% Propensity-matched 3-year overall survival rate (AJCC 7th ed. multiple imputation set): I: 30.6% C: 6.6% Log-rank test: p=0.003 -- Propensity-matched 3-year median overall survival (AJCC 8th ed. multiple imputation set): I: 17 months (95%CI: 12.5-21.5) C: 10 months (95%CI: 8.5-11.5) Propensity-matched 1-year overall survival rate (AJCC 8th ed. multiple imputation set): I: 61.2% C: 41.8%	

						Propensity-matched 2-year overall survival rate (AJCC 8th ed. multiple imputation set): I: 37.7% C: 12.6% Propensity-matched 3-year overall survival rate (AJCC 8th ed. multiple imputation set): I: 28.3% C: 4.2% Log-rank test: p=0.008 -- <u>Prognostic variables for 3-year overall survival from multivariable analysis in propensity-matched group (ACJJ 7th ed. complete case set):</u> **Resection [reference group = yes]:** HR=0.567 (95%CI: 0.346-0.926) Other variables in the multivariable model: - **Age (≥65 year):** HR=2.618 (95%CI: 1.501-4.569) - N1:HR=1.188 (95%CI: 0.680-2.075) - **Multiple lesions:** HR=1.890 (95%CI: 1.083-3.298) - Vascular invasion:HR=1.367 (95%CI: 0.777-2.406)	

Notes:

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

8. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

Author, year	**Selection of participants** **Was selection of exposed and non-exposed cohorts drawn from the same population?**	**Exposure** **Can we be confident in the assessment of exposure?**	**Outcome of interest** **Can we be confident that the outcome of interest was not present at start of study?**	**Confounding-assessment** **Can we be confident in the assessment of confounding factors?**	**Confounding-analysis** **Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?**	**Assessment of outcome** **Can we be confident in the assessment of outcome?**	**Follow up** **Was the follow up of cohorts adequate? In particular, was outcome data complete or imputed?**	**Co-interventions** **Were co-interventions similar between groups?**	**Overall Risk of bias**
	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Definitely yes, probably yes, probably no, definitely no	Low, Some concerns, High
Moustafa 2019	*Definitely yes* Reason: SEER database was used, data is based on a nation-wide cancer registry (USA)	*Probably yes* Reason: Treatment is recorded in the SEER registry (see: https://seer.cancer.gov/registries/cancer_regis	*Definitely yes* Reason: The event in the primary outcome (overall survival) is death due to any cause (which is a hard outcome). Death	*Definitely yes* Reason: Variables are part of the SEER database/ cancer registry	*Probably yes* Reason: Authors used propensity matching based on a logistic regression containing several relevant characteristics (i.e. age, race, T, lymph	*Definitely yes* Reason: Deaths are recorded in the SEER database/ cancer registry	*Probably yes* Reason: Imputed for some analyses, but no indication provided whether de data was	*Probably no* Reason: Both intervention have different natures with different patterns of morbidities. No iformation is provided on co-	**Some concerns**

		try/data_collection.html)	(or cause of death) is also recorded in the SEER registry.		node status, multifocality, vascular invasion, cause of death). Some potentially relevant characteristics were not available in the SEER database which could have prognostic impact, for example: periductal infiltration, mass forming, mixed mass forming, periductal infiltrating growth pattern, surgical margin status,		missing completely at random or not	interventions. It is plausible that different co-interventions were provided because of the different nature/morbidity patterns of both interventions. Furthermore, it is unclear whether those (different) co-interventions would have a relation with the outcome (i.e. overall survival).	

Implementatieplan bij module 9 Indicatie resectie

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Aanbeveling 1 Verricht de beoordeling voor resectie van een galweg- of galblaascarcinoom in een centrum met chirurgische expertise van het galweg- en galblaascarcinoom.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn Onderwijs aan differentianten chirurgie	Wetenschappelijke verenigingen	
Aanbeveling 2 Verricht geen resectie van het galweg- of galblaascarcinoom bij patiënten met metastasen (stadium IV). Hieronder vallen ook positieve extraregionale lymfklieren waaronder die bij de truncus coeliacus en in het aortocavale window.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn Onderwijs aan differentianten chirurgie	Wetenschappelijke verenigingen	

Aanbeveling 3 Laat iedere patiënt met een galweg- of galblaascarcinoom in aanmerking komen voor resectie wanneer een complete (R0) resectie mogelijk lijkt.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn Onderwijs aan differentianten chirurgie	Wetenschappelijke verenigingen	
Aanbeveling 4 Verricht een diagnostische laparoscopie voorafgaand aan een laparotomie bij alle patiënten met galweg- of galblaascarcinoom.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn Onderwijs aan differentianten chirurgie	Wetenschappelijke verenigingen	
Aanbeveling 5 Verricht niet standaard een resectie bij patiënten met intrahepatisch cholangiocarcinoom en multifocale ziekte in de lever of positieve lymfklieren.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn Onderwijs aan differentianten chirurgie	Wetenschappelijke verenigingen	
Aanbeveling 6	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn	Wetenschappelijke verenigingen	

Verricht niet standaard een resectie bij patiënten met perihilair cholangiocarcinoom en meer dan 180 graden betrokkenheid van de arteria hepatica naar de toekomstige restlever of positieve lymfklieren.					Onderwijs aan differentianten chirurgie		
<u>Aanbeveling 7</u> Verricht niet standaard een resectie bij patiënten met galblaaskanker en een stille icterus bij presentatie of bij patiënten met positieve lymfklieren.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn Onderwijs aan differentianten chirurgie	Wetenschappelijke verenigingen	
<u>Aanbeveling 8</u> Voer geen cholecystectomie en follow-up uit bij patiënten met een galblaaspoliep ≤ 5 millimeter.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn Onderwijs aan differentianten chirurgie Onderwijs aan de eerste lijn over	Wetenschappelijke verenigingen	

Verricht een één- tot maximaal twee-jarige echografische follow-up bij patiënten met een galblaaspoliep tussen 6-10 millimeter. Verricht een cholecystectomie bij patiënten met een galblaaspoliep >10 millimeter, poliepen die meer dan 3 millimeter per jaar groeien en in patiënten met primaire scleroserende cholangitis (PSC). Verricht geen cholecystectomie indien er een echografisch beeld is van adenomyomatosis, ook niet bij afwijkingen >1 centimeter.					poliepen (wel of niet verwijzen)		
<u>Aanbeveling 9</u> Heroverweeg een resectie bij patiënten met een lokaal gevorderd	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn Onderwijs aan differentianten chirurgie	Wetenschappelijke verenigingen	

galweg- of galblaascarcinoom en een goede response op systemische chemotherapie.							

Table of excluded studies

Autor and year	Reason
Abbas S, Sandroussi C. Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. HPB (Oxford). 2013 Jul;15(7):492-503. doi: 10.1111/j.1477-2574.2012.00616.x. Epub 2013 Jan 8. PMID: 23750491; PMCID: PMC3692018.	Concerns the extent of surgery: surgery + vascular resection vs surgery alone
Ashai N, Prasad P, Rajdev L. Multimodality Management of Localized Biliary Cancer. Curr Treat Options Oncol. 2019 May 29;20(7):58. doi: 10.1007/s11864-019-0655-0. PMID: 31144050.	Narrative/opinion statement
Bai T, Chen J, Xie ZB, Ma L, Liu JJ, Zhu SL, Wu FX, Li LQ. Combined portal vein resection for hilar cholangiocarcinoma. International Journal of Clinical and Experimental Medicine. 2015;8(11):21044.	combined portal vein resection vs hepatectomy
Baltatzis M, Jegatheeswaran S, Siriwardena AK. Neoadjuvant chemoradiotherapy before resection of perihilar cholangiocarcinoma: A systematic review. Hepatobiliary Pancreat Dis Int. 2020 Apr;19(2):103-108. doi: 10.1016/j.hbpd.2020.02.007. Epub 2020 Feb 20. PMID: 32147487.	Seems to report outcomes non-comparatively only
Benjamin AJ, Suss NR, Roggin KK, Bentrem DJ, Talamonti MS, Baker MS. Neoadjuvant chemotherapy is associated with higher rates of margin negative resection and improved survival in patients with extrahepatic cholangiocarcinoma. Gastroenterology. 2017 Apr 1;152(5):S1238-9.	Conference abstract
Bolton NM, Solomon D, Leigh N, Feingold D, Magge D, Golas B, Labow D, Sarpel U. 669-10 Year Experience with Gallbladder Carcinoma in a High Volume Center: Pathologic	Conference abstract

Variables, Survival and Patterns of Recurrence. Gastroenterology. 2018 May 1;154(6):S-1278.	
Bourgouin S, Ewald J, Mancini J, Moutardier V, Delpero JR, Le Treut YP. Predictors of Survival in Ampullary, Bile Duct and Duodenal Cancers Following Pancreaticoduodenectomy: a 10-Year Multicentre Analysis. J Gastrointest Surg. 2015 Jul;19(7):1247-55. doi: 10.1007/s11605-015-2833-0. Epub 2015 May 7. PMID: 25947547.	All patients received surgery
Bouzid C, Kheloufi M, Salmi A, Sedkaoui C, Cherchar K, Boubnider M, Smail N, Bentabak K. Adjuvant chemotherapy did not improve gallbladder cancer prognosis. HPB. 2019 Jan 1;21:S991-2.	Conference abstract
Buettner S, Koerkamp BG, Ejaz A, Buisman FE, Kim Y, Margonis GA, Alexandrescu S, Marques HP, Lamelas J, Aldrighetti L, Gamblin TC, Maithel SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Marsh JW, IJzermans JN, Pawlik TM. The effect of preoperative chemotherapy treatment in surgically treated intrahepatic cholangiocarcinoma patients-A multi-institutional analysis. J Surg Oncol. 2017 Mar;115(3):312-318. doi: 10.1002/jso.24524. Epub 2017 Jan 20. PMID: 28105651.	Wrong comparison
Buettner S, Wilson A, Margonis GA, Gani F, Ethun CG, Poultsides GA, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Maithel SK, Pawlik TM. Assessing Trends in Palliative Surgery for Extrahepatic Biliary Malignancies: A 15-Year Multicenter Study. J Gastrointest Surg. 2016 Aug;20(8):1444-52. doi: 10.1007/s11605-016-3155-6. Epub 2016 Apr 27. PMID: 27121233; PMCID: PMC5450034.	Uncorrected
Cercek A, Boerner T, Tan BR, Chou JF, Gönen M, Boucher TM, Hauser HF, Do RKG, Lowery MA, Harding JJ, Varghese AM, Reidy-Lagunes D, Saltz L, Schultz N, Kingham TP, D'Angelica MI, DeMatteo RP, Drebin JA, Allen PJ, Balachandran VP, Lim KH, Sanchez-Vega F, Vachharajani N, Majella Doyle MB, Fields RC, Hawkins WG, Strasberg SM, Chapman WC, Diaz LA Jr, Kemeny NE, Jarnagin WR. Assessment of Hepatic Arterial Infusion of Floxuridine in Combination With Systemic Gemcitabine and Oxaliplatin in Patients With Unresectable Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol. 2020 Jan 1;6(1):60-67. doi: 10.1001/jamaoncol.2019.3718. PMID: 31670750; PMCID: PMC6824231.	Single-arm cohort
Cercek A, Kemeny NE, Boerner T, Tan BR, Chou JF, Gonen M, Boucher TM, Hauser H, Do RK, Lowery MA, Kingham P. A bi-institutional phase II study of hepatic arterial	Conference abstract

infusion (HAI) with floxuridine (FUDR) and dexamethasone (Dex) combined with systemic gemcitabine and oxaliplatin (GemOx) for unresectable intrahepatic cholangiocarcinoma (ICC).	
Chen W, Ke K, Chen YL. Combined portal vein resection in the treatment of hilar cholangiocarcinoma: a systematic review and meta-analysis. Eur J Surg Oncol. 2014 May;40(5):489-495. doi: 10.1016/j.ejso.2014.02.231. Epub 2014 Feb 28. PMID: 24685155.	Portal vein resection; all studies have a control group, unclear which treatment was provided for control groups
Chi, Ctr Inr 2017	Unable to identify this study
Cloyd JM, Ejaz A, Pawlik TM. The Landmark Series: Intrahepatic Cholangiocarcinoma. Ann Surg Oncol. 2020 Aug;27(8):2859-2865. doi: 10.1245/s10434-020-08621-4. Epub 2020 May 17. PMID: 32419038.	Review, potentially useful for considerations
D'Souza MA, Valdimarsson VT, Campagnaro T, Cauchy F, Chatzizacharias NA, D'Hondt M, Dasari B, Ferrero A, Franken LC, Fusai G, Guglielmi A, Hagendoorn J, Hidalgo Salinas C, Hoogwater FJH, Jorba R, Karanjia N, Knoefel WT, Kron P, Lahiri R, Langella S, Le Roy B, Lehwald-Tywuschik N, Lesurtel M, Li J, Lodge JPA, Martinou E, Molenaar IQ, Nikov A, Poves I, Rassam F, Russolillo N, Soubrane O, Stättner S, van Dam RM, van Gulik TM, Serrablo A, Gallagher TM, Sturesson C; E-AHPBA scientific and research committee. Hepatopancreatoduodenectomy -a controversial treatment for bile duct and gallbladder cancer from a European perspective. HPB (Oxford). 2020 Sep;22(9):1339-1348. doi: 10.1016/j.hpb.2019.12.008. Epub 2019 Dec 30. PMID: 31899044.	Case-series concerning hepatopancreaticoduodenectomy
Dasari BVM, Ionescu MI, Pawlik TM, Hodson J, Sutcliffe RP, Roberts KJ, Muiesan P, Isaac J, Marudanayagam R, Mirza DF. Outcomes of surgical resection of gallbladder cancer in patients presenting with jaundice: A systematic review and meta-analysis. J Surg Oncol. 2018 Sep;118(3):477-485. doi: 10.1002/jso.25186. PMID: 30259519.	resection in patients with jaundice vs no jaundice
Edeline J, Touchefeu Y, Guiu B, Farge O, Tougeron D, Baumgaertner I, Ayav A, Campillo-Gimenez B, Beuzit L, Pracht M, Lièvre A, Le Sourd S, Boudjema K, Rolland Y, Boucher E, Garin E. Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol. 2020 Jan 1;6(1):51-59. doi: 10.1001/jamaoncol.2019.3702. PMID: 31670746; PMCID: PMC6824230.	Single-arm, SIRT+CT
Engineer R, Goel M, Chopra S, Patil P, Purandare N, Rangarajan V, Ph R, Bal M, Shrikhande S, Shrivastava SK, Mehta S. Neoadjuvant Chemoradiation Followed by Surgery for Locally Advanced Gallbladder Cancers: A New Paradigm. Ann Surg Oncol.	Non-comparative

2016 Sep;23(9):3009-15. doi: 10.1245/s10434-016-5197-0. Epub 2016 Apr 13. PMID: 27075323.	
Engineer R, Patkar S, Lewis SC, Sharma AD, Shetty N, Ostwal V, Ramaswamy A, Chopra S, Agrawal A, Patil P, Mehta S, Goel M. A phase III randomised clinical trial of perioperative therapy (neoadjuvant chemotherapy versus chemoradiotherapy) in locally advanced gallbladder cancers (POLCAGB): study protocol. BMJ Open. 2019 Jun 27;9(6):e028147. doi: 10.1136/bmjopen-2018-028147. PMID: 31253621; PMCID: PMC6609079.	Study protocol
Ettrich TJ, Berger AW, Seufferlein T, Perkhofer L. Liposomal irinotecan (nal-IRI) plus 5-fluorouracil (5-FU) and leucovorin (LV) or gemcitabine plus cisplatin in advanced cholangiocarcinoma: The AIO-NIFE-trial, an open label, randomized, multicenter phase II trial.	Poster abstract (JAMANETWORK)
Gamboa AC, Maithel SK. The Landmark Series: Gallbladder Cancer. Ann Surg Oncol. 2020 Aug;27(8):2846-2858. doi: 10.1245/s10434-020-08654-9. Epub 2020 May 30. PMID: 32474816.	Review, potentially useful for considerations
Goetze T., Paolucci V., Al-Batran S.-E, Incidental gallbladder cancer - Neoadjuvant randomized multicenter Phase III - GAINTrial of the AIO/CALGP/ACO in Germany and 1st. Line trial in trial concept - Based on the "The German-Registry" network, European Surgical Research 2019 60 Supplement 1 (2-3)	Conference abstract
Goetze TO, Bechstein WO, Bankstahl US, Keck T, Königsrainer A, Lang SA, Pauligk C, Piso P, Vogel A, Al-Batran SE. Neoadjuvant chemotherapy with gemcitabine plus cisplatin followed by radical liver resection versus immediate radical liver resection alone with or without adjuvant chemotherapy in incidentally detected gallbladder carcinoma after simple cholecystectomy or in front of radical resection of BTC (ICC/ECC) - a phase III study of the German registry of incidental gallbladder carcinoma platform (GR)- the AIO/ CALGP/ ACO- GAIN-trial. BMC Cancer. 2020 Feb 14;20(1):122. doi: 10.1186/s12885-020-6610-4. PMID: 32059704; PMCID: PMC7023745.	Study protocol
Götze TO, Paolucci V, Al-Batran SE. “The German-Registry” of incidental gallbladder cancer and the GAIN-phase III trial: Transformation from a registry to treatment platform due to a trial in trial concept. Annals of Oncology. 2018 Oct 1;29:viii263.	Poster presentation
Grendar J, Grendarova P, Sinha R, Dixon E. Neoadjuvant therapy for downstaging of locally advanced hilar cholangiocarcinoma: a systematic review. HPB (Oxford). 2014	Concerns neoadj treatment + survery, seems to report outcomes non-comparatively for the intervention/comparison of interest

Apr;16(4):297-303. doi: 10.1111/hpb.12150. Epub 2013 Aug 26. PMID: 23981000; PMCID: PMC3967880.	
Guzailinur A., Lin H., Dai Z., Fang Z., Effect Analysis of Surgical Management Combined with Doxorubicin in the Treatment of Gallbladder Carcinoma, Anti-Tumor Pharmacy 2018 8:6 (935-938)	Article in Chinese (See EMBASE additional information)
Hakeem AR, Papoulas M, Menon KV. The role of neoadjuvant chemotherapy or chemoradiotherapy for advanced gallbladder cancer–a systematic review. European Journal of Surgical Oncology. 2019 Feb 1;45(2):83-91.	Concerns neoadj treatment + surgery, seems to report outcomes non-comparatively for the intervention/comparison of interest
Huguet JM, Lobo M, Labrador JM, Boix C, Albert C, Ferrer-Barceló L, Durá AB, Suárez P, Iranzo I, Gil-Raga M, de Burgos CB, Sempere J. Diagnostic-therapeutic management of bile duct cancer. World J Clin Cases. 2019 Jul 26;7(14):1732-1752. doi: 10.12998/wjcc.v7.i14.1732. PMID: 31417920; PMCID: PMC6692271.	Review, potentially useful for considerations
Kamarajah S, Giovinazzo F, Roberts KJ, Punia P, Sutcliffe RP, Marudanayagam R, Chatzizacharias N, Isaac J, Mirza DF, Muiesan P, Dasari BV. The role of down staging treatment in the management of locally advanced intrahepatic cholangiocarcinoma: Review of literature and pooled analysis. Ann Hepatobiliary Pancreat Surg. 2020 Feb;24(1):6-16. doi: 10.14701/ahbps.2020.24.1.6. Epub 2020 Feb 27. PMID: 32181423; PMCID: PMC7061034.	Includes non-comparative designs, GRADE applied per study instead of per outcome
Komaya K, Ebata T, Shirai K, Ohira S, Morofuji N, Akutagawa A, Yamaguchi R, Nagino M; Nagoya Surgical Oncology Group. Recurrence after resection with curative intent for distal cholangiocarcinoma. Br J Surg. 2017 Mar;104(4):426-433. doi: 10.1002/bjs.10452. Epub 2017 Jan 31. PMID: 28138968.	All patients received surgery, potentially useful for considerations -> predictors for survival
Kovalenko YA, Zharikov YO, Konchina NA, Gurmikov BN, Marinova LA, Zhao AV. Perihilar cholangiocarcinoma: A different concept for radical resection. Surg Oncol. 2020 Jun;33:270-275. doi: 10.1016/j.suronc.2020.02.013. Epub 2020 Feb 17. PMID: 32561092.	All patients underwent resection
Ku D, Tang R, Pang T, Pleass H, Richardson A, Yuen L, Lam V. Survival outcomes of hepatic resections in Bismuth-Corlette type IV cholangiocarcinoma. ANZ J Surg. 2020 Sep;90(9):1604-1614. doi: 10.1111/ans.15531. Epub 2019 Dec 15. PMID: 31840387.	All patients underwent hepatic resections
Kuipers H, de Savornin Lohman EAJ, van Dooren M, Braat AE, Daams F, van Dam R, Erdmann JI, Hagendoorn J, Hoogwater FJH, Groot Koerkamp B, van Gulik TM, de Reuver PR, de Boer MT. Extended Resections for Advanced Gallbladder Cancer: Results from a Nationwide Cohort Study. Ann Surg Oncol. 2021 Feb;28(2):835-843. doi:	All patients received surgery, potentially useful for considerations

10.1245/s10434-020-08858-z. Epub 2020 Jul 21. PMID: 32696306; PMCID: PMC7801314.	
Lee SE, Kim SW, Han HS, Lee WJ, Yoon DS, Cho BH, Choi IS, Kim HJ, Hong SC, Lee SM, Choi DW, Park SJ, Kim HJ, Jang JY; Korean Pancreas Surgery Club. Surgical Strategy for T2 Gallbladder Cancer: Nationwide Multicenter Survey in Korea. J Korean Med Sci. 2018 May 30;33(28):e186. doi: 10.3346/jkms.2018.33.e186. PMID: 29983693; PMCID: PMC6033102.	Extended cholecystectomy vs simple cholecystectomy
Liu F, Li FY. Role of tumour location and surgical extent on prognosis in T2 gallbladder cancer: an international multicentre study. Br J Surg. 2020 Nov;107(12):e632. doi: 10.1002/bjs.11938. Epub 2020 Sep 21. PMID: 32955123.	Correspondence
Martin RCG 2nd, Simo KA, Hansen P, Rocha F, Philips P, McMasters KM, Tatum CM, Kelly LR, Driscoll M, Sharma VR, Crocenzi TS, Scoggins CR. Drug-Eluting Bead, Irinotecan Therapy of Unresectable Intrahepatic Cholangiocarcinoma (DELTIC) with Concomitant Systemic Gemcitabine and Cisplatin. Ann Surg Oncol. 2022 Sep;29(9):5462-5473. doi: 10.1245/s10434-022-11932-3. Epub 2022 Jun 3. PMID: 35657463.	Meeting abstract (web of science)
Molina V, Ferrer-Fábrega J, Sampson-Dávila J, Díaz A, Ayuso C, Forner A, Fondevila C, García-Valdecasas JC, Bruix J, Fuster J. Intention-to-treat curative liver resection in patients with "very early" intrahepatic cholangiocarcinoma. Langenbecks Arch Surg. 2020 Nov;405(7):967-975. doi: 10.1007/s00423-020-01958-0. Epub 2020 Aug 17. PMID: 32804283.	All patients underwent resection
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Nemunaitis JM, Brown-Glabeman U, Soares H, Belmonte J, Liem B, Nir I, Phuoc V, Gullapalli RR. Gallbladder cancer: review of a rare orphan gastrointestinal cancer with a focus on populations of New Mexico. BMC Cancer. 2018 Jun 18;18(1):665. doi: 10.1186/s12885-018-4575-3. PMID: 29914418; PMCID: PMC6006713.	Narrative review
Riby D, Mazzotta AD, Bergeat D, Verdure L, Sulpice L, Bourien H, Lièvre A, Rolland Y, Garin E, Boudjema K, Edeline J. Downstaging with Radioembolization or Chemotherapy for Initially Unresectable Intrahepatic Cholangiocarcinoma. Ann Surg Oncol. 2020	Wrong comparison, analyses downstaging treatment together (SIRT+CT) in multivar: downstaging-treatment in multi-var analysis not associated with better or worse prognosis

Oct;27(10):3729-3737. doi: 10.1245/s10434-020-08486-7. Epub 2020 May 29. PMID: 32472411.	
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Singh SK, Talwar R, Kannan N, Tyagi AK, Jaiswal P, Kumar A. Aggressive Surgical Approach for Gallbladder Cancer: a Single-Center Experience from Northern India. J Gastrointest Cancer. 2015 Dec;46(4):399-407. doi: 10.1007/s12029-015-9766-4. PMID: 26410686.	Not corrected for confounding
Singh SK, Talwar R, Kannan N, Tyagi AK, Jaiswal P, Kumar A. Patterns of Presentation, Treatment, and Survival Rates of Gallbladder Cancer: a Prospective Study at a Tertiary Care Centre. J Gastrointest Cancer. 2018 Sep;49(3):268-274. doi: 10.1007/s12029-017-9940-y. PMID: 28367607.	Not corrected for confounding
Tran TB, Ethun CG, Pawlik TM, Schmidt C, Beal EW, Fields RC, Krasnick B, Weber SM, Salem A, Martin RCG, Scoggins CR, Shen P, Mogal HD, Idrees K, Isom CA, Hatzaras I, Shenoy R, Maithel SK, Poultsides GA. Actual 5-Year Survivors After Surgical Resection of Hilar Cholangiocarcinoma. Ann Surg Oncol. 2019 Feb;26(2):611-618. doi: 10.1245/s10434-018-7075-4. Epub 2018 Dec 11. PMID: 30539494.	All patients underwent resection
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Vasilieva L, Papadhimitriou SI, Alexopoulou A, Kostopoulos I, Papiris K, Pavlidis D, Xinopoulos D, Romanos A, Dourakis SP. Clinical presentation, diagnosis, and survival in cholangiocarcinoma: A prospective study. Arab J Gastroenterol. 2016 Dec;17(4):181-184. doi: 10.1016/j.ajg.2016.10.003. Epub 2016 Nov 30. PMID: 27914884.	Uncorrected
Wagner A, Wiedmann M, Tannapfel A, Mayr C, Kiesslich T, Wolkersdörfer GW, Berr F, Hauss J, Witzigmann H. Neoadjuvant Down-Sizing of Hilar Cholangiocarcinoma with Photodynamic Therapy--Long-Term Outcome of a Phase II Pilot Study. Int J Mol Sci. 2015 Nov 6;16(11):26619-28. doi: 10.3390/ijms161125978. PMID: 26561801; PMCID: PMC4661837.	Preoperative photodynamic therapy (wrong intervention)
Wellner UF, Shen Y, Keck T, Jin W, Xu Z. The survival outcome and prognostic factors for distal cholangiocarcinoma following surgical resection: a meta-analysis for the 5-	All patients underwent surgery, factors associated with survival after surgery

year survival. Surg Today. 2017 Mar;47(3):271-279. doi: 10.1007/s00595-016-1362-0. Epub 2016 May 28. PMID: 27236779.	
Yousaf A, Kim JU, Eliahoo J, Taylor-Robinson SD, Khan SA. Ablative Therapy for Unresectable Intrahepatic Cholangiocarcinoma: A Systematic Review and Meta-Analysis. J Clin Exp Hepatol. 2019 Nov-Dec;9(6):740-748. doi: 10.1016/j.jceh.2019.08.001. Epub 2019 Aug 19. PMID: 31889756; PMCID: PMC6926226.	Searches for papers with ablative therapies, instead of chemotherapy/surgery
Zaidi MY, Abou-Alfa GK, Ethun CG, Shrikhande SV, Goel M, Nervi B, Primrose J, Valle JW, Maithel SK. Evaluation and management of incidental gallbladder cancer. Chin Clin Oncol. 2019 Aug;8(4):37. doi: 10.21037/cco.2019.07.01. Epub 2019 Aug 5. PMID: 31431030; PMCID: PMC8289444.	Narrative review

Literature search strategy

Systematic reviews

Embase.com	481	471
Medline Ovid	251	76
Total	**732**	**547**

New references: 81

Embase.com

'biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR 'bile duct') NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ab,ti,kw AND [english]/lim AND [2012-2019]/py NOT 'conference abstract':it NOT ([animals]/lim NOT [humans]/lim) AND ('systematic review'/exp OR 'meta analysis'/exp OR (((systematic*) NEAR/3 (review)) OR meta-analy* OR metaanaly*):ab,ti,kw)

Medline Ovid

exp Gallbladder Neoplasms/ or exp biliary tract neoplasms/ or exp bile duct neoplasms/ or exp cholangiocarcinoma/ or exp klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile duct) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ab,ti,kf. AND english.la. AND (2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020) NOT (exp animals/ NOT humans/) AND (Systematic Review/ OR Meta-Analysis/ OR (((systematic*) ADJ3 (review)) OR meta-analy* OR metaanaly*).ab,ti,kf.)

Trials

Database searched	**via**	**Years of coverage**	**Records**	**Records after duplicates removed**
Embase	Embase.com	1971 - Present	767	760
Medline ALL	Ovid	1946 - Present	422	80
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	643	464
Total			**1832**	**1304**

Embase 766

('biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin*):ti,kw) AND [english]/lim AND [2015-2030]/py NOT 'conference abstract':it NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) AND (('clinical trial'/exp OR (trial):ab,ti,kw) OR [clinical trial number]/lim)

Medline Ovid 422

(exp *Gallbladder Neoplasms/ or exp *biliary tract neoplasms/ or exp *bile duct neoplasms/ or exp *cholangiocarcinoma/ or exp *klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ti,kf.) AND english.la. AND 2015:2030.(sa_year). NOT (exp animals/ NOT humans/) AND ((Clinical Trial/ OR (trial).ab,ti,kf.) OR clinicaltrials.si.)

Cochrane (2015-2020) 643
((((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ti)

Module 10 Adjuvante systemische behandeling

Uitgangsvraag
Wat is de plaats van adjuvante systemische behandeling bij patiënten met galweg- of galblaascarcinoom na chirurgische resectie?

Inleiding
De meerderheid van de patiënten die een curatieve resectie heeft ondergaan voor een cholangiocarcinoom of een galblaascarcinoom, ontwikkelt binnen twee jaar na de operatie een lokaal recidief of metastasen op afstand (Belkouz, 2019). Er zijn individuele inschattingen mogelijk voor de overleving na resectie door middel van een nomogram of predictiemodel voor patiënten met een perihilair cholangiocarcinoom, distaal cholangiocarcinoom, intrahepatisch cholangiocarcinoom of galblaascarcinoom.
Gezien de hoge kans op een recidief is er behoefte aan een aanvullende behandeling om de kans op een recidief te verkleinen of het optreden van het recidief uit te stellen. Hiervoor zijn verschillende gerandomiseerde studies verricht. De vraag van dit hoofdstuk van de richtlijn is om deze studies te onderzoeken op effectiviteit en toepasbaarheid op de Nederlands situatie.

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

What are the benefits and risks of adjuvant systemic treatment compared with no adjuvant systemic treatment for patients who underwent resection for cholangiocarcinoma or gallbladder cancer with curative intent?

P: patients who underwent resection for cholangiocarcinoma or gallbladder cancer with curative intent
I: adjuvant systemic treatment, with or without concurrent radiotherapy
C: no systemic treatment
O: critical: overall survival, quality of life
important: disease-free survival, toxicity

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

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

The working group defined the following minimal clinically (patient) relevant differences (using the PASKWIL criteria for adjuvant treatment where possible):

- Overall survival: > 5% difference between the groups or > 3% difference and HR < 0.7, at least three years of median follow-up time
- Quality of life: A minimal clinically important difference of 10 points on the quality-of-life instrument EORTC QLQ-C30 or a difference of a similar magnitude on other quality of life instruments.
- Disease-free survival: HR < 0.6

- Toxicity: ≥ 5% difference in lethal adverse events and ≥ 25% difference in serious (grade ≥3) adverse events

Search and select (Methods)

For the update of this guideline, two broad systematic literature searches were performed to identify relevant publications involving patients with biliary tract cancer. First, the databases Medline (via OVID) and Embase (via Embase.com) were searched using relevant search terms for systematic reviews published between January 1st 2012 and December 31st 2019 for Medline, and between January 1st 2012 and August 31rd 2020 for Embase. Second, the databases Medline (via OVID), Embase (via Embase.com) and Cochrane Central Register of Controlled Trials (via Wiley) were searched for RCTs published between January 1st 2015 and October 12th 2020. The detailed search strategies are depicted under the tab Methods.

The systematic literature searches resulted in 547 unique hits for systematic reviews and 1304 unique hits for RCTs. A preselection of systematic reviews and RCTs based on study population and study design was made. In case of doubt about the eligibility of a particular publication, this publication was included in the preselection. Potentially relevant studies were divided into four categories: diagnosis, surgery, systemic treatment, and other treatment options. The preselection in the category 'systemic treatment' included 773 hits. Subsequently, publications were screened based on title and abstract using the following selection criteria: (a) full-text publication in English or Dutch; (b) systematic review or RCT; (c) involving patients who underwent resection for cholangiocarcinoma or gallbladder carcinoma with curative intent; and (d) comparing at least one of the aforementioned outcome measures between patients who received adjuvant systemic therapy and patients who received no adjuvant systemic therapy. This resulted in 20 systematic reviews and 8 RCTs. After reading the full text, one systematic review was included in the analysis of the literature. A table with reasons for exclusion is presented under the tab Methods.

Results

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

Summary of literature

Description of studies

Luvira (2021) published a Cochrane review providing an overview on the benefits and harms of postoperative adjuvant chemotherapy for resectable cholangiocarcinoma. Electronic searches were performed in the 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 for trials to identify relevant studies up to 28 April 2021. Eligible trials included adults who underwent curative-intent resection of cholangiocarcinoma. The diagnosis had to be confirmed by pathological examination of surgical specimens. All regimens of adjuvant chemotherapy were eligible and could be compared against no adjuvant treatment (surgery alone), placebo, or a different regimen or form of chemotherapy. For the current clinical question, only the comparison between adjuvant chemotherapy versus no adjuvant chemotherapy is relevant.

Relevant outcomes reported in the review by Luvira (2021) were “all-cause mortality”, defined as the number of people who died at five years, “cancer-related mortality”, “serious adverse events”, as defined by the ICH guidelines for Good Clinical Practice, “health-related quality of life”, as reported by the participants and as assessed by standard grading systems measured on a valid scale, and “time to recurrence of the tumor”. Where available, we extracted additional data on overall survival, quality of life, disease-free survival or toxicity from the original studies.

Four of the RCTs included in the review by Luvira (2021) provided a comparison between adjuvant chemotherapy versus no adjuvant chemotherapy (Takada, 2002; Ebata, 2018; Edeline, 2019; Primrose, 2019). Chemotherapy regimens used included mitomycin-C and 5-FU (Takada, 2002), gemcitabine (Ebata, 2018), gemcitabine plus oxaliplatin (Edeline, 2019), and capecitabine (Primrose, 2019). None of the interventions involved concurrent radiotherapy.
These studies were performed in Japan (n=2), France (n=1), and the United Kingdom (n=1). Patients in the study by Takada (2002) were included between 1986-1992, the other studies included patients more recently, between 2006 and 2014. The review by Luvira (2021) only extracted data for patients with cholangiocarcinoma, 867 in total. The trials by Takada (2002), Edeline (2019) and Primrose (2019) also included patients with gallbladder carcinoma. We extracted these data from the original studies and added the data to this literature summary. Takada (2002) included 436 patients with pancreatobiliary carcinoma, 118 of these patients had bile duct carcinoma and were included in the analysis by Luvira (2021), while 112 patients had gallbladder carcinoma. Ebata (2018) included 225 patients with extrahepatic bile duct cancer (45% perihilar, 55% distal). Edeline (2019) included 194 patients with biliary tract cancer (intrahepatic 44%, perihilar 8%, distal 28%, gallbladder 20%). Primrose (2019) included 447 patients with biliary tract cancer (intrahepatic 19%, hilar 29%, muscle-invasive gallbladder 18%, lower common bile duct cholangiocarcinoma 35%).

The authors of the review (Luvira, 2021) judged all four trials to be at overall high risk of bias, using a tool with three answer categories: ‘low risk of bias’, ‘unclear risk of bias’ and ‘high risk of bias’. Risk of bias was related to incomplete information about allocation sequence generation and concealment (Edeline, 2019; Takada, 2002), lack of blinding in all four trials, and reporting bias could not be assessed for the study of Takada (2002) because no protocol was available.
We performed our own risk of bias assessment using a tool with four answer categories (‘Definitely yes’, ‘Probably yes’, ‘Probably no’, and ‘Definitely no’). We had some concerns about the studies of Takada (2002) and Primrose (2019), while the risk of bias in the studies by Ebata (2018) and Edeline (2019) was judged to be low.
The discrepancy between the two assessments was related to the use of different answer categories. For the items about random sequence generation and allocation concealment, Luvira (2021) selected ‘unclear risk of bias’ for two studies where we selected ‘probably yes’.

For one of the RCTs included in the review by Luvira (2021), the BILCAP study (Primrose, 2019), long term results on overall survival and disease-free survival were published (Bridgewater, 2021).

Results

Overall survival

The review by Luvira (2021) presented a meta-analysis for patients with cholangiocarcinoma. Data from this meta-analysis are presented below under the heading 'Cholangiocarcinoma' Where available, data regarding patients with gallbladder carcinoma (Takada, 2002) or a mixed population of patients with cholangiocarcinoma or gallbladder carcinoma (Edeline, 2019; Primrose, 2019; Bridgewater, 20221) were extracted from the original trials and are presented under the headings 'Gallbladder carcinoma' and 'Cholangiocarcinoma and gallbladder carcinoma'.

Cholangiocarcinoma

All four trials reported five-year survival of patients with cholangiocarcinoma, median follow-up time was more than three years. The review by Luvira (2021) converted these data to all-cause mortality at five years. In the group receiving adjuvant chemotherapy, 236 out of 437 patients had died after five years (54.0%). In the group receiving no adjuvant chemotherapy, 255 out of 430 patients had died after five years (59.3%). The risk difference was -0.05 [95%CI -0.11 to 0.01]. This difference fulfills the minimal clinically (patient) relevant difference of >5% difference between the groups.

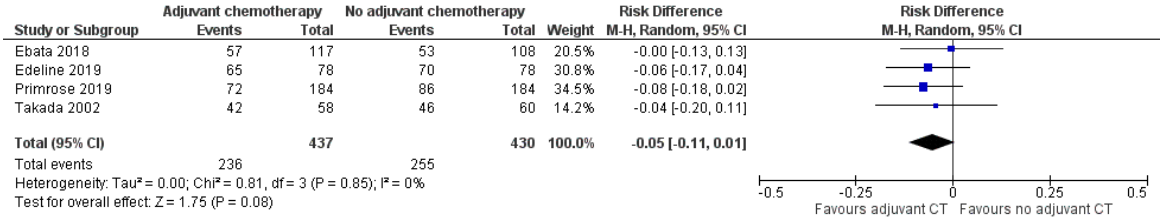

Figure 1: Forest plot of all-cause mortality at five years

Gallbladder carcinoma

The study by Takada (2002) also reported five-year survival for gallbladder carcinoma. In the group receiving adjuvant mitomycin C and 5-fluorouracil, the five-year survival rate was 26.0%. In the group receiving no adjuvant chemotherapy, the five-year survival rate was 14.4% (p=0.04). This difference fulfills the minimal clinically (patient) relevant difference of > 5% difference between the groups.

Cholangiocarcinoma and gallbladder carcinoma

The study by Edeline (2019) included both patients with cholangiocarcinoma and gallbladder carcinoma. Data were reported only for all patients together. Overall survival rates at 48 months were 51% in the group that received adjuvant gemcitabine and oxaliplatin versus 52% in the group that did not receive adjuvant chemotherapy. The hazard ratio for all patients was 1.08 (95%CI 0.70 to 1.66). This HR did not fulfill the minimal clinically relevant difference of a HR < 0.7 between the groups.

The study by Primrose (2019) also included patients with gallbladder carcinoma. Data were reported for all patients (cholangiocarcinoma and gallbladder carcinoma), not separately for gallbladder carcinoma. The hazard ratio for all patients (cholangiocarcinoma and gallbladder carcinoma) was 0.81 (95%CI 0.63 to 1.04; p=0.097). No absolute difference between the groups was reported, the hazard ratio did not fulfill the minimal clinically (patient) relevant difference of a HR < 0.7 between the groups.

The publication by Bridgewater (2021) reported all-cause mortality in the BILCAP study after a median follow-up of 106 months (95%CI 98 to 108 months). These data involve patients

with cholangiocarcinoma and gallbladder carcinoma. The hazard ratio (adjusted for the stratification factors resection status, performance status and site of disease) was 0.84 (95%CI 0.67 to 1.06). This difference does not fulfill the minimal clinically (patient) relevant difference of a HR < 0.7 between the groups.

Quality of life
Two RCTs reported on health-related quality of life (Edeline, 2019; Primrose, 2019), both used the EORTC QLQ-C30 questionnaires. Edeline (2019) reported the time to definitive deterioration and found no statistically significant differences between the groups. Reported data did not include a comparison of scores in both groups and therefore no judgement of the clinical relevance of any differences (>10 points) could be made. Primrose (2019) reported median (IQR) standardised area under the curve, interpreted as the average monthly quality of life. No differences >10 points were reported for any of the functional or symptoms scales.

Disease-free survival
The original studies included in the review by Luvira (2021) reported data on disease-free survival (Takada, 2002), relapse-free survival (Ebata, 2018; Edeline, 2019), and recurrence-free survival (Primrose, 2019; Bridgewater, 2021).

Takada (2002) reported that for patients with cholangiocarcinoma, five-year disease-free survival rate was 20.7% in the group that received adjuvant mitomycin C and 5-fluorouracil and 15.0% in the group that did not receive adjuvant chemotherapy. For patients with gallbladder carcinoma, five-year disease-free survival rate was 20.3% in the group that received adjuvant mitomycin C and 5-fluorouracil and 11.6% in the group that did not receive adjuvant chemotherapy. No hazard ratio was reported, so it was not possible to assess whether these differences fulfilled the minimal clinically (patient) relevant difference of HR < 0.6.

In the study by Ebata (2018), five-year relapse-free survival rates were 45.7% in the group that received adjuvant gemcitabine and 44.0% in the group that did not receive adjuvant chemotherapy. The HR for relapse in patients receiving adjuvant gemcitabine, compared with no adjuvant chemotherapy, was 0.93 (95%CI 0.66 to 1.32; p=0.693). This difference does not fulfill the minimal clinically (patient) relevant difference of HR < 0.6.

In the study by Edeline (2019), relapse-free survival rates were 66% versus 64% at 12 months, 53% versus 46% at 24 months, 47% versus 43% at 36 months, and 36% versus 33% at 48 months in the groups that received gemcitabine and oxaliplatin versus no adjuvant chemotherapy. The hazard ratio for relapse-free survival was 0.88 (95%CI 0.62 to 1.25). This difference does not fulfill the minimal clinically (patient) relevant difference of HR < 0.6.

The long-term results of the BILCAP study (Bridgewater, 2021) showed a median recurrence-free survival of 24.3 months (95%CI 18.6 to 34.6 months) in the group that received adjuvant capecitabine and 17.4 months (95%CI 11.8 to 23.0 months) in the group that did not receive adjuvant chemotherapy. The hazard ratio (adjusted for the minimization factors resection status, performance status and site of disease) was 0.81 (95%CI 0.65 to 1.01). This difference does not fulfill the minimal clinically (patient) relevant difference of HR < 0.6.

Toxicity
Ebata (2018) assessed serious adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. For four categories of grade 3

or 4 serious events, all haematological events, a statistically significant difference was found between the groups (leucocytes 29.2% vs 1.9%; p<0.001, neutrophils 58.4% vs. 3.8%; p<0.001, haemoglobin 7.1% vs 0.9%; p=0.036 and platelets 7.1% vs 0%, p=0.007). The differences for leucocytes and neutrophils fulfill the minimal clinically (patient) relevant difference of 25%.

Edeline (2019) also assessed serious adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), except for neurotoxicity, which was assessed using Levi's scale. For four grade 3 or 4 laboratory serious adverse events, statistically significant differences were found between the groups: neutrophil decrease 17% vs 0%; p<0.001, platelets decrease 7% vs 0%, p=0.01; alkaline phosphatase increase 9% vs 2%, p=0.05; and GGT increase 37% vs 14%; p<0.001. For two grade 3 or 4 clinical serious adverse events, statistically significant differences were found between the groups: peripheral sensory neuropathy (18% vs 0%, p<0.001), and asthenia (8% vs 0%, p=0.01). None of these differences fulfilled the minimal clinically (patient) relevant diference of 25%.

Level of evidence of the literature

The evidence was derived from (a systematic review of) RCTs, therefore the level of evidence for all outcomes started at 'high'. The authors of the Cochrane review performed a GRADE assessment and downgraded three levels to 'very low' for both overall survival and toxicity. However, this risk of bias was mainly caused by 'performance and detection bias' because these trials did not use placebo in the arm that did not receive adjuvant chemotherapy. For an objective outcome as overall survival, this assessment was deemed to be too strict and a new GRADE assessment was performed.

The level of evidence regarding the outcome measure **overall survival** was downgraded by two levels because of conflicting results (-1 inconsistency, unexplained heterogeneity) and the number of included patients (-1 imprecision, because the pooled confidence interval includes the possibility of no difference).

The level of evidence regarding the outcome measure **quality of life** was downgraded by two levels because of study limitations (-1 risk of bias, because of lack of blinding); number of included patients (-1 imprecision, because this was a single trial including a total of 447 patients).

The level of evidence regarding the outcome measure **disease-free survival** was downgraded by one level because of number of included patients (-1 imprecision, because the confidence interval included the possibility of a clinically relevant difference).

The level of evidence regarding the outcome measure **toxicity** was downgraded by one level because of the number of included patients (-1 imprecision, because there were two trials including a total of 415 patients).

Conclusions

LOW GRADE	Adjuvant systemic chemotherapy may increase **overall survival** when compared with no adjuvant systemic chemotherapy in patients who

	underwent resection for cholangiocarcinoma or gallbladder carcinoma with curative intent. *Source: Takada, 2002; Ebata, 2018; Edeline, 2019; Primrose, 2019; Bridgewater, 2021; Luvira, 2021;*

Adjuvant systemic chemotherapy involved mitomycin C and 5-fluorouracil, gemcitabine, gemcitabine and oxaliplatin, and capecitabine.

Low GRADE	Adjuvant systemic chemotherapy may not reduce or increase **quality of life** when compared with no adjuvant systemic chemotherapy in patients who underwent resection for cholangiocarcinoma or gallbladder carcinoma with curative intent. *Source: Primrose, 2019; Luvira, 2021;*

Adjuvant systemic chemotherapy involved capecitabine.

Moderate GRADE	Adjuvant systemic chemotherapy may not reduce or increase **disease-free survival** when compared with no adjuvant systemic chemotherapy in patients who underwent resection for cholangiocarcinoma or gallbladder carcinoma with curative intent. *Source: Takada, 2002; Ebata, 2018; Edeline, 2019; Bridgewater, 2021;*

Adjuvant systemic chemotherapy involved mitomycin C and 5-fluorouracil, gemcitabine, gemcitabine and oxaliplatin, and capecitabine.

Moderate GRADE	Adjuvant systemic chemotherapy likely increases **(haematological) toxicity,** when compared with no adjuvant systemic chemotherapy in patients who underwent resection for cholangiocarcinoma or gallbladder carcinoma with curative intent. *Source: Ebata, 2018; Edeline, 2019;*

Adjuvant systemic chemotherapy involved gemcitabine, and gemcitabine and oxaliplatin.

Overwegingen – van bewijs naar aanbeveling

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

De Cochrane review van Luvira (2021) includeerde vier RCT's waarin een vergelijking werd onderzocht tussen patiënten die wel of geen adjuvante systemische chemotherapie kregen na een resectie met curatieve intentie van galweg- en galblaaskanker. Vooral op 5-FU of gemcitabine gebaseerde behandelschema's zijn onderzocht, gezien de ervaring met deze behandelingen in de palliatieve setting. Voor beide cruciale uitkomstmaten, overleving en kwaliteit van leven, werd informatie gerapporteerd.

De 1e RCT vergeleek mitomycine C + 5-FU met observatie in 139 patiënten met galwegcarcinoom en 140 patiënten met galblaascarcinoom (Takada, 2002). Voor

galblaascarcinoom was de 5-jaars overleving beter met adjuvante chemotherapie; 26,0% versus 14,4% (p=0,04). Voor galwegcarcinoom was er geen verschil in 5-jaars overleving; 26,7% versus 24,1%. De 2e RCT vergeleek gemcitabine met observatie in 225 patiënten met perihilair cholangiocarcinoom (pCCA) of distaal cholangiocarcinoom (dCCA) (Ebata, 2018). De mediane overleving was gelijk in beide armen; HR 1,01; 95% CI: 0,70-1,45. De 3e RCT vergeleek gemcitabine + oxaliplatin met observatie in 196 patiënten met galweg- of galblaascarcinoom (Edeline, 2019). De mediane overleving was gelijk in beide armen; HR 1,08; 95% CI: 0,70-1,66. De 4e RCT vergeleek capecitabine met observatie in 447 patiënten met galweg- of galblaascarcinoom (Bridgewater, 2022). De mediane overleving was vergelijkbaar in beide armen in de lange termijn resultaten; HR 0,85; 95% CI: 0,67-1,06). In een per-protocol analyse met correctie voor lymfklier status, tumor graad en geslacht was de HR voor OS 0,74 met 95% CI 0,59-0,94. Zelfs in deze per-protocol analyse is de HR > 0,70.

Kwaliteit van leven werd in twee studies gerapporteerd, in één studie konden de resultaten langs de lat van klinische relevantie worden gelegd; geen van de subschalen op de EORTC QLQ-C30 liet een klinisch relevant verschil tussen de groepen zien. De bewijskracht was laag.

Daarnaast werden er ook resultaten gerapporteerd voor ziektevrije overleving en toxiciteit. Ziektevrije overleving werd gerapporteerd in alle vier de RCT's en de lange-termijn follow-up publicatie van de BILCAP-studie (Bridgewater, 2021). In geen van deze studies werd een klinisch relevant verschil in ziektevrije overleving gerapporteerd. De bewijskracht was redelijk.

Toxiciteit (graad 3-4) werd in twee RCT's gerapporteerd. In de ene studie (Ebata, 2018) kwamen vier hematologische ernstige bijwerkingen statistisch significant vaker voor in de groep die adjuvante chemotherapie kreeg (leukopenie, neutropenie, anemie, en trombocytopenie). Voor leukopenie en neutropenie was dit verschil tussen de groepen groter dan 25% (29,2% versus 1,9% en 58,4% versus 3,8%). In de andere studie (Edeline, 2019) waren er op basis van laboratoriumbepalingen vier ernstige bijwerkingen die statistisch significant vaker voorkwamen in de groep die adjuvante chemotherapie kreeg (neutropenie, trombocytopenie, stijging van alkaline fosfatase, stijging van GGT). Daarnaast kwamen perifere sensorische neuropathie en asthenie statistisch significant vaker voor in de groep die adjuvante chemotherapie kreeg. De bewijskracht was redelijk.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>
Gezien het hoge risico op een recidief is er wel een duidelijk wens naar adjuvante behandeling, zowel bij de artsen als ook bij patiënten. Dat er weinig bewijs is voor adjuvante behandeling, levert soms dilemma's op bij patiënten met een hoog risico op recidief en bij jonge patiënten. Het is belangrijk om de gevolgen van systemische therapie te bespreken met de patiënt, denk hierbij bijvoorbeeld aan (ernstige) hand-voet syndroom, vermoeidheid, diarree, buikpijn en/ of misselijkheid bij capecitabine (Primrose, 2019).

<u>Kosten (middelenbeslag)</u>
In Nederland worden geen adjuvante behandelingen gegeven voor galwegcarcinoom na resectie. Hierbij is geen kostenafweging gemaakt, maar alleen een inhoudelijke keuze gemaakt op basis van onvoldoende effectiviteit. De kosten van bij voorbeeld capecitabine zelf zijn niet hoog, daarbij komen echter nog de kosten van begeleiding op de polikliniek door een medisch oncoloog.

<u>Aanvaardbaarheid, haalbaarheid en implementatie</u>

De beperkte en onzekere overlevingswinst voor adjuvante behandeling rechtvaardigt het standaard gebruik van adjuvante behandeling niet. Dit is in overeenstemming met de huidige zorg.

Aanbeveling

Aanbeveling-1

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

De beperkte winst van adjuvante behandeling zoals gevonden in de reeds verrichte studies is de hoofdreden om geen adjuvante behandeling te adviseren.

Geef geen adjuvante behandeling na een in opzet curatieve resectie van een galweg- of galblaascarcinoom.

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Bijlagen bij module 10 Adjuvante systemische behandeling

Evidence tables

Evidence table for systematic review of RCTs (intervention studies)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Luvira, 2021 [individual study characteristics deduced from Luvira, 2021 unless otherwise indicated]	SR and meta-analysis of RCTs *Literature search up to 28 April 2021* **A**: Takada, 2002 **B**: Ebata, 2018 **C**: Edeline, 2019 **D**: Primrose, 2019 (with additional information available in **E:** Bridgewater, 2021) Parallel-group design <u>Setting and country:</u> **A**: 31 centres, Japan **B**: 48 hospitals, Japan	Inclusion criteria: - RCTs - 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 - diagnosis of cholangiocarcinoma was	Postoperative adjuvant chemotherapy **A**: mitomycin-C 6 mg/m2 on day of surgery, 5-FU 310 mg/m2 2 courses for 5 consecutive days (during postoperative weeks 1 and 3), 5-FU (orally) daily **B**: gemcitabine 1000 mg/m2 over 30 minutes on day 1, 8 and 15 followed by a rest period of 1 week **C**: gemcitabine 1000 mg/m2 over 100 minutes on day 1, oxaliplatin 85 mg/m2 over 2 hours on day 2 every 2 weeks for 12 cycles **D**: capecitabine 1250 mg/m2 twice a day on days 1 to 14 of a 3-weekly cycle for 24 weeks	No postoperative adjuvant chemotherapy	<u>End-point of follow-up:</u> **A**: 5 years **B**: median of 79.4 months **C**: median of 46.5 months **D**: median of 60 months <u>For how many patients were no complete outcome data available:</u> **A**: none **B**: two **C**: none **D**: none	<u>All-cause mortality:</u> Number of people who died at five years *Cholangiocarcinoma* **A**: I: 42/58 (72%) / C: 46/60 (77%); RD -0.04 [95%CI -0.20 to 0.11] **B**: I: 57/117 (49%) / C: 53/108 (49%); RD 0.00 [95%CI -0.13 to 0.13] **C**: I: 65/78 (83%) / C: 70/78 (90%); RD -0.06 [95%CI -0.17 to 0.04] **D**: 72/184 (39%) / C: 86/184 (47%); RD -0.08 [95%CI 0.18 to 0.02] Pooled effect (random effects model): RD -0.05 [95% CI -0.11 to 0.01] favoring adjuvant systemic chemotherapy Heterogeneity (I^2): 0%	<u>Review authors' conclusion:</u> 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

	C: 33 centres, France **D**: 44 specialist hepato-pancreato-biliary centres, United Kingdom <u>Source of funding[a]:</u> **A**: Not stated **B**: Nagoya Surgery Support Organization and Eli Lilly Japan K.K. **C**: Programme Hospitalier de Recherche Clinique (PHRC 2009) and Ligue Nationale Contre le Cancer **D**: Cancer Research UK and Roche (advisory role in study design) <u>Conflicts of interests[a]</u>: **A:** not stated **B:** none reported **C:** several conflicts of interest reported **D:** several conflicts of interest reported	established by pathological examination of surgical specimens *5 studies included, four of which provided a comparison between adjuvant systemic chemotherapy versus no adjuvant systemic chemotherapy* <u>N</u> **A**: 508, 139 of which had bile duct carcinoma **B**: 225 **C**: 196 **D**: 447 <u>Tumour location[a], n (%)</u> **A:** bile duct carcinoma 118 (100%) **B:** perihilar 102 (45%), distal 123 (55%) **C:** intrahepatic 86 (44%), perihilar 15 (8%), distal 55 (28%), gallbladder 38 (20%) **D:** intrahepatic 84 (19%), hilar 128 (29%), muscle-invasive				<u>Five-year survival rates[a]</u> *Gallbladder carcinoma* **A:** I: 26.0% / C: 14.4% <u>Five-year mortality and hazard ratio[a]</u> *Cholangiocarcinoma and gallbladder carcinoma* **C:** I: 43% / C: 41%; HR 1.078 (95% CI 0.699 to 1.663) **D:** I: 51% / C: 58% HR 0.81 (95% CI 0.63 to 1.04; p=0.097) **E:** I: 65% / C: 71% <u>Quality of life[a]</u> **D:** *QLQ-C30 functioning scales, median (IQR) standardised area under the curve* Physical I: 82.5 (64.0 to 92.7) / C: 85.0 (70.0 to 93.3); p=0.16 Role I: 72.9 (50.5 to 91.7) / C: 81.3 (52.8 to 91.7); p=0.18 Emotional 79.9 (58.9 to 92.2) / C: 83.3 (64.8 to 93.2); p=0.36 Cognitive I: 87.5 (66.1 to 96.4) / C: 87.5 (76.0 to 100); p=0.1 Social	overall high risk of bias, and imprecision. There is a need for further randomised clinical trials designed to be at low risk of bias and with adequate sample size exploring the best adjuvant chemotherapy treatment after surgery in people with cholangiocarcinoma.

		gallbladder 79 (18%), lower common bile duct cholangiocarcinoma 156 (35%)				I: 76.2 (56.9 to 91.7) / C: 83.3 (64.6 to 95.8); p=0.0060 Global health status or quality of life I: 67.9 (52.1 to 80.6) / C: 70.8 (56.3 to 83.3); p=0.18 *QLQ-C30 symptoms scales* Fatigue I: 27.8 (15.0-43.3) / C: 27.1 (11.1 to 38.9); p=0.27 Nausea and vomiting I: 2.8 (0.0 to 11.3) / C: 1.4 (0.0 to 8.3); p=0.27 Pain I: 17.7 (5.2 to 38.2) / C: 16.7 (6.3 to 33.3); p=0.8 Dyspnoea I: 6.3 (0.0 to 25.0) / C: 8.3 (0.0-25.0); p=0.43 Insomnia I: 21.9 (4.9 to 44.1) / C: 20.8 (5.6 to 41.7); p=0.8 Appetite loss I: 6.3 (0.0 to 18.8) / C: 8.3 (0.0 to 20.8); p=0.88 Constipation I: 4.2 (0.0 to 22.9) / C: 2.1 (0.0 to 16.7); p=0.62 Diarrhoea I: 8.3 (0.0 to 16.7) / C: 4.2 (0.0 to 16.7); p=0.36 Financial difficulties I: 2.1 (0.0 to 22.2) / C: 0.0 (0.0 to 18.8); p=0.35 <u>Disease-free survival[ab]</u> **A:** five-year disease-free survival rate cholangiocarcinoma	

						I: 20.7% / C: 15.0% five-year disease-free survival rate gallbladder carcinoma I: 20.3% / C: 11.6% **B:** five-year relapse-free survival rate cholangiocarcinoma I: 45.7% / C: 44.0% HR 0.93 (95%CI 0.66 to 1.32; p=0.693) **C:** relapse-free survival rate 12 months I: 66% / C: 64% 24 months I: 53% / C: 46% 36 months I: 47% / C: 43% 48 months I: 36% / C: 33% HR 0.880 (95%CI 0.620 to 1.249) **D:** disease recurrence rate I: 60% / C: 65% 0-24 months HR 0.75 (95%CI 0.58 to 0.98; p=0.033) 24-60 months HR 1.48 (95%CI 0.80 to 2.77; p=0.21) **E:** HR 0.81 (95%CI 0.65 to 1.01), adjusted for resection status, performance status and site of disease <u>Toxicity (serious adverse events)[a]:</u> Number of people experiencing serious adverse events **B**: Haematological toxicity grade 3 or 4[a] , n (%) Leucocytes I: 33 (29.2%) / C: 2 (1.9%); p<0.001	

						Neutrophils I: 66 (58.4%) / C: 4 (3.8%); p<0.001 Haemoglobin I: 8 (7.1%) / C: 1 (0.9%); p=0.036 Platelets I: 8 (7.1%) / C: 0; p=0.007 AST I: 2 (1.8%) / C: 2 (1.9%); p=1.000 ALT I: 1 (0.9%) / C: 1 (0.9%); p=1.000 Bilirubin I: 0 / C: 4 (3.8%); p=0.053 Creatinine I: 0 / C: 0; p=1.000 Non-haematological toxicity grade 3 or 4[a], n (%) Fatigue I: 6 (5.3%) / C: 1 (0.9%); p=0.120 Anorexia I: 6 (5.3%) / C: 2 (1.9%); p=0.282 Nausea I: 1 (0.9%) / C: 0; p=1.000 Vomiting I: 1 (0.9%) / C: 1 (0.9%); p=1.000 Diarrhoea I: 0 / C: 0; p=1.000 Fever I: 4 (3.5%) / C: 0; p=0.122 Febrile neutropenia I: 0 / C: 0; p=1.000	

[a] Data extracted from the original study
[b] Data extracted from the additional publication on the BILCAP trial by Bridgewater (2021)

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

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Luvira, 2021	Yes	Yes Search period and strategy are described and multiple databases were searched	Yes	Yes Characteristics relevant to the PICO were reported	Not applicable	Yes	Yes	Yes	Yes Conflicts of interest were reported for the review No Source of funding and conflicts of interest were not reported for the studies included in the review

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

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

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

Research question: What are the benefits and risks of adjuvant systemic treatment compared with no adjuvant systemic treatment for patients who underwent resection for cholangiocarcinoma with curative intent?

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Takada, 2002	Probably yes; Reason: A randomized design, stratified	No information;	Definitely no; Reason: The control group was not treated	Probably yes; Reason: An intention to treat analysis was performed, 98% of	Probably yes; Reason: All outcomes described in the Methods section are	Probably no; Reason: The sample size calculation was based on an assumed	**Some concerns** (overall survival, disease-free survival)

	according to institution and disease, was used		with any drugs including placebo	eligible patients were included in the analysis	reported in the Results section	difference of 20% in 5-year survival rate between the groups (15% in the control group). The number of eligible patients was unbalanced between the treatment arms for gallbladder carcinoma (I:69/C:43)	
Ebata, 2018	Probably yes; Reason: Patients were assigned randomly by a modified minimization method	Definitely yes; Reason: Treatment allocation was performed centrally through a web-based randomization system managed by the data centre	Definitely no; Reason: open-label study	Definitely yes; Reason: An intention to treat analysis was performed, 225/226 patients were included in the analysis	Probably yes; Reason: All outcomes described in the Methods section are reported in the Results section	Probably no; Reason: the target sample size of 300 was not reached	**LOW** (overall survival, disease-free survival, toxicity
Edeline, 2019	Probably yes; Reason: Randomization with minimization was stratified by primary site	Probably yes; Reason: No explicit information, but a randomization procedure with minimization is performed at the time of allocation and therefore it will be difficult to impossible to predict which group the patient will be allocated to	Definitely no; Reason: open-label study	Definitely yes; Reason: An intention to treat analysis was performed, 194/196 patients were included in the analysis	Probably yes; Reason: All outcomes described in the Methods section are reported in the Results section	Probably yes; Reason: no other issues noted	**LOW** (overall survival, disease-free survival, toxicity)
Primrose, 2019 Bridgewater, 2021	Definitely yes; Reason: A computerized algorithm was used	Probably yes; Reason: Allocation was centrally generated and broken by	Definitely no; Reason: treatments were not blinded	Probably no; Reason: An intention to treat analysis was performed, all eligible	Definitely yes; Reason: All outcomes defined in the study protocol were	No information; Reason: intention-to-treat and per protocol analyses are reported,	**Some concerns** (overall survival, quality of life, disease-free survival)

		telephone. Although it was not reported who was aware of the allocation scheme generated from the computer, it seems unlikely that care providers can estimate the allocation through the system and cause selection bias		patients were included in the analysis	reported in the manuscript	however these analyses provide too little descriptions for intercurrent events (and how these were handled) to assess if any other risk of bias was present The funder of the study has an advisory role in study design but no role in the running of the study, data collection, data analysis, data interpretation, or writing of the report	

Randomization: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
Allocation concealment: refers to the protection (blinding) of the randomization process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomization (performed at a site remote from trial location). Inadequate procedures are all procedures based on inadequate randomization procedures or open allocation schedules..
Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments, but this should not affect the risk of bias judgement. Blinding of those assessing and collecting outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment or data collection (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is usually not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary. Finally, data analysts should be blinded to patient assignment to prevents that knowledge of patient assignment influences data analysis.
Lost to follow-up: If the percentage of patients lost to follow-up or the percentage of missing outcome data is large, or differs between treatment groups, or the reasons for loss to follow-up or missing outcome data differ between treatment groups, bias is likely unless the proportion of missing outcomes compared with observed event risk is not enough to have an important impact on the intervention effect estimate or appropriate imputation methods have been used.
Selective outcome reporting: Results of all predefined outcome measures should be reported; if the protocol is available (in publication or trial registry), then outcomes in the protocol and published report can be compared; if not, outcomes listed in the methods section of an article can be compared with those whose results are reported.
Other biases: Problems may include: a potential source of bias related to the specific study design used (e.g. lead-time bias or survivor bias); trial stopped early due to some data-dependent process (including formal stopping rules); relevant baseline imbalance between intervention groups; claims of fraudulent behavior; deviations from intention-to-treat (ITT) analysis; (the role of the) funding body (see also downgrading due to industry funding https://kennisinstituut.viadesk.com/do/document?id=1607796-646f63756d656e74). Note: The principles of an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.
Overall judgement of risk of bias per study and per outcome measure, including predicted direction of bias (e.g. favors experimental, or favors comparator). Note: the decision to downgrade the certainty of the evidence for a particular outcome measure is taken based on the body of evidence, i.e. considering potential bias and its impact on the certainty of the evidence in all included studies reporting on the outcome.

Implementatieplan bij module 10 Adjuvante systemische behandeling

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Geef geen adjuvante behandeling na een in opzet curatieve resectie van een galweg- of galblaascarcinoom.	< 1 jaar	Geen	Bekendheid met richtlijn	Buiten Nederland is adjuvante therapie wel standaard zorg. Dit zal tot weerstand bij patiënten en behandelaren kunnen leiden.	Publicatie richtlijn	Wetenschappelijke verenigingen	Er zullen studies aankomen in adjuvante setting.

Table of excluded studies

Reference	Reason for exclusion
Reviews	
Messina, 2019	Review including more RCTs available
Kish, 2020	Review including more RCTs available
Ke 2020	Review of retrospective studies
Shroff, 2019	Wrong publication type: clinical guideline
Manterola, 2019	Review of retrospective studies
Suzuki, 2019	Narrative review
Wang, 2019	Review of retrospective studies
Ma, 2019	Review of retrospective studies
Horgan, 2018	Narrative review
Kim, 2018	Review of retrospective studies
Acharya, 2017	Wrong population: periampullary adenocarcinoma
Ghidini, 2017	Review including retrospective studies
Doherty, 2016	Review of retrospective studies
Kwon, 2015	Review of retrospective studies
Ma, 2015	Review of retrospective studies
Zhu, 2014	Wrong population: periampullary adenocarcinoma
Williams, 2014	Narrative review
Wei, 2013	Wrong comparison
Horgan, 2012	Review including retrospective studies
RCTs	
Ebata, 2018	Included in the review by Luvira (2021)
Edeline, 2019	Included in the review by Luvira (2021)
Kobayashi, 2019	Included in the review by Luvira (2021)
Primrose, 2019	Included in the review by Luvira (2021)
Seita, 2020	Wrong study design
Sharma, 2019	Wrong comparison
Siebenhüner, 2018	Wrong study design
Terajima, 2018	Wrong publication type: abstract

Literature search strategy

Systematic reviews

Embase.com	481	471
Medline Ovid	251	76
Total	**732**	**547**

New references: 81

Embase.com
'biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR 'bile duct') NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ab,ti,kw AND (english)/lim AND (2012-2019)/py NOT 'conference abstract':it NOT ((animals)/lim NOT (humans)/lim) AND ('systematic review'/exp OR 'meta analysis'/exp OR (((systematic*) NEAR/3 (review)) OR meta-analy* OR metaanaly*):ab,ti,kw)

Medline Ovid
exp Gallbladder Neoplasms/ or exp biliary tract neoplasms/ or exp bile duct neoplasms/ or exp cholangiocarcinoma/ or exp klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile duct) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ab,ti,kf. AND english.la. AND (2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020) NOT (exp animals/ NOT humans/) AND (Systematic Review/ OR Meta-Analysis/ OR (((systematic*) ADJ3 (review)) OR meta-analy* OR metaanaly*).ab,ti,kf.)

Trials

Database searched	via	Years of coverage	Records	Records after duplicates removed
Embase	Embase.com	1971 - Present	767	760
Medline ALL	Ovid	1946 - Present	422	80
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	643	464
Total			**1832**	**1304**

Embase 766
('biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin*):ti,kw) AND (english)/lim AND (2015-2030)/py NOT 'conference abstract':it NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) AND (('clinical trial'/exp OR (trial):ab,ti,kw) OR (clinical trial number)/lim)

Medline Ovid 422
(exp *Gallbladder Neoplasms/ or exp *biliary tract neoplasms/ or exp *bile duct neoplasms/ or exp *cholangiocarcinoma/ or exp *klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ti,kf.) AND english.la. AND 2015:2030.(sa_year). NOT (exp animals/ NOT humans/) AND ((Clinical Trial/ OR (trial).ab,ti,kf.) OR clinicaltrials.si.)

Cochrane (2015-2020) 643
((((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ti)

Module 11 Palliatieve systemische behandeling in de 1e lijn

Uitgangsvraag
Wat is de rol van eerstelijns palliatieve systemische therapie bij patiënten met een lokaal uitgebreid of gemetastaseerd galweg- of galblaascarcinoom?

Inleiding
Meer dan twee-derde van de patiënten met galweg-of galblaascarcinoom komt niet in aanmerking voor een in opzet curatieve resectie omdat er sprake is van een lokaal uitgebreide tumor of omdat er metastasen op afstand zijn. In de Nederlandse richtlijn uit 2013 werd een combinatie van gemcitabine met cisplatin als eerstelijns palliatieve systemische therapie geadviseerd indien de conditie dit toeliet. Dit advies is gebaseerd op de ABC-02 trial die een voordeel in overleving liet zien van 12 maanden na gemcitabine met cisplatin vergeleken met 8 maanden na alleen gemcitabine (HR 0,64; 95% CI: 0,52-0,80) (Valle, 2010). Sindsdien zijn er diverse trials uitgevoerd naar een verscheidenheid aan systemische regimes, met of zonder doelgerichte therapieën of immuuntherapieën. Doel van deze module is adviezen te formuleren met medenemen van de nieuwe trials welke systemische behandeling de voorkeur heeft bij patiënten met een lokaal uitgebreid galweg- of galblaascarcinoom. Ook wordt er beschreven welk diagnostisch onderzoek toegepast wordt om maligniteit aan te tonen alvorens palliatieve systeemtherapie te starten.

Search and select
A systematic review of the literature was performed to answer the following question:
What are the (un)beneficial effects of systemic first-line palliative systemic therapy in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma?

P: patients with non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma
I: systemic therapy other than gemcitabine combined with cisplatin or oxaliplatin only or no systemic therapy
C: gemcitabine combined with cisplatin or oxaliplatin
O: overall survival, quality of life, progression-free survival, toxicity

Relevant outcome measures
The working group considered overall survival and quality of life as critical outcome measures for decision making; and progression-free survival and toxicity as important outcome measures for decision making.

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

The working group defined a minimal clinically important difference as follows:
(using the PASKWIL criteria for palliative treatment with OS standard arm ≤ 12 months and > 12 months where possible and other criteria):

OS standard arm ≤ 12 months:
- Overall survival: absolute difference in OS > 12 weeks and hazard ratio (HR) < 0.7.
- Quality of life: absolute difference ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other disease-specific quality of life questionnaires.

- Toxicity: ≥ 5% difference in fatal adverse events, ≥ 25% difference in grade ≥ 3 adverse events.

OS standard arm > 12 months:
- Overall survival: absolute difference in OS of > 16 weeks and HR < 0.7.
- Quality of life: absolute difference ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other disease-specific quality of life questionnaires.
- Progression-free survival: absolute difference in OS of > 16 weeks and HR < 0.7.
- Toxicity: ≥ 5% difference in lethal adverse events and ≥ 25% difference in serious (grade ≥3) adverse events

Search and select (Methods)
A broad systematic literature search was performed to identify relevant publications involving patients with biliary tract cancer. The databases Medline (via OVID) and Embase (via Embase.com) were searched for systematic reviews with relevant search terms until August 31, 2021. Medline (via OVID) and Embase (via Embase.com) were also searched until 12-01-2021 for trials with relevant search terms. The detailed search strategy is depicted under the tab Methods. The systematic literature searches resulted in 1861 hits (547 systematic reviews and 1304 RCTs).

A preselection of systematic reviews and RCTs was made by advisors from the Knowledge Institute of the Dutch Association of Medical Specialists, based on study population and study design. An inclusive approach was followed, in case of any doubt about the eligibility of a publication, the publication was included in the preselection. In total, 74 systematic reviews related to palliative systemic treatment were included in the preselection.

Subsequently, publications were screened based on title and abstract using the following selection criteria: (a) full-text publication in English or Dutch; (b) systematic review of RCTs; (c) involving patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma; and (d) comparing at least one of the aforementioned outcome measures between patients who received palliative systemic therapy and patients who received another regimen of palliative systemic therapy or no palliative systemic therapy. This resulted in 31 systematic reviews.

After reading the full text, one systematic review including a network meta-analysis was selected (Li, 2019). The guideline working group was aware of another, more recent, systematic review that also included a network meta-analysis (Jiang, 2021). After analysis of both reviews, the working group decided to select the more recent review by Jiang (2021) and supplement this with two studies (Leone, 2016; Vogel, 2018) that were included in the review by Li (2019) but not in the review by Jiang (2021). The reason these studies were not included in the review by Jiang (2021) is that these studies were focused on a patient population with a specific gene mutation, which was an exclusion criterion in the review by Jiang (2021).

The preselection also included 38 RCTs. These publications were screened based on title and abstract using the following selection criteria: (a) full text publication in English or Dutch; (b) RCT; (c) involving patients with a locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma; and (d) comparing at least one of the aforementioned outcome measures between patients who received gemcitabine combined with cisplatin or oxaliplatin and patients who received systemic therapy other than gemcitabine combined with cisplatin or oxaliplatin only or no systemic therapy. After reading the full text, all 38 studies were

excluded (see the table with reasons for exclusions under the tab Methods). The guideline working group was aware of two recent RCTs providing relevant information (Oh, 2022; Kelley, 2023). In total, the literature summary includes one systematic review and four RCTs.

Results
One systematic review (Jiang (2021)) and four additional RCTs (Leone, 2016; Vogel, 2018; Oh, 2022; Kelley, 2023) were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature
Description of studies

Leone (2016) conducted a randomized controlled phase II trial (the Vecti-BIL study) of patients with KRAS wild-type advanced biliary tract cancer in 12 Italian university hospitals and cancer institutes. Patients were randomized (1:1) to receive either gemcitabine (1000 mg/m^2), oxaliplatin (100 mg/m^2) and panitumumab (6 mg/kg) (n=45) or gemcitabine (1000 mg/m^2) and oxaliplatin (100 mg/m^2) (n=44). Outcome measures included progression-free survival, overall survival, and toxicity.

Vogel (2018) conducted a randomized controlled phase II trial (the PICCA study) of patients with KRAS wild-type advanced biliary cancer in Germany. Patients were randomized (2:1) to receive either gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) with panitumumab (9 mg/kg) (n=62) or gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) (n=28). Outcome measures included overall survival, progression-free survival and toxicity.

Oh (2022) conducted a randomized controlled phase III trial (the TOPAZ-1 trial) in 17 countries in Asia, Europe, North America, and South America. Patients were randomized (1:1) to receive either gemcitabine (1000 mg/m^2), cisplatin (25 mg/m^2) and durvalumab (1500 mg) (n=341) or gemcitabine (1000 mg/m^2), cisplatin (25 mg/m^2), and placebo (n=344). Outcome measures included overall survival, progression-free survival, and toxicity.

Kelley (2023) conducted a randomized controlled phase III trial (the KEYNOTE-966 trial) in 175 centres in Asia-Pacific, Europe, North America, and South America. Patients were randomized (1:1) to receive gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) and either pembrolizumab (n=533) or placebo (n=536). Outcome measures included overall survival, progression-free survival, and toxicity.

The systematic review and network meta-analysis by **Jiang (2021)** included RCTs published between 2010 and 2020 on patients with advanced biliary tract carcinoma who received first-line chemotherapy. The diagnosis had to be confirmed by histology. Outcome measures should include overall survival, progression-free survival, overall response rate, or adverse events (grade ≥3 neutropenia, vomiting, diarrhea, and fatigue). Studies focused on a patient population with specific gene mutations were excluded from the review.
Twenty-four studies were included in the review, two of which were retrospective cohort studies which is noteworthy as the inclusion criteria state that studies should be phase II or III RCTs. The authors of the review did not provide an explanation why these studies were included. These 24 studies involved a total of 3,555 patients and twenty different regimens of first-line treatment, including:

- best supportive care;

- chemotherapy mono-therapy (n=2; gemcitabine or S-1);
- chemotherapy combination treatment (n=10; 5-FU + leucovorin (FUFA), gemcitabine + oxaliplatin, capecitabine + oxaliplatin, gemcitabine + cisplatin, irinotecan + cisplatin, gemcitabine + S1, 5-FU + oxaliplatin, S1 + cisplatin, gemcitabine + cisplatin + S1, gemcitabine + capecitabine + oxaliplatin);
- chemotherapy and targeted therapy (n=6; gemcitabine + cisplatin + cediranib, gemcitabine + oxaliplatin + erlotinib, gemcitabine + oxaliplatin + cetuximab, gemcitabine + sorafenib, gemcitabine + cisplatin + ramucirumab, gemcitabine + cisplatin + merestinib)
- chemoradiotherapy (n=1; 5-FU + cisplatin + radiotherapy)

The current clinical question is focused on the comparison between gemcitabine and cisplatin or gemcitabine and oxaliplatin with best supportive care or any of the other regimens.
The systematic review by Jiang (2021) included 10 studies in which gemcitabine + cisplatin was used in one of the treatment arms. Direct comparisons were available for the following regimens:

(1) gemcitabine + cisplatin + cediranib (Valle, 2015);
(2) gemcitabine monotherapy (Valle, 2010; Okusaka, 2010);
(3) irinotecan + cisplatin (Dos Santos, 2020);
(4) gemcitabine + S1 (Huang, 2015; Morizane, 2019);
(5) gemcitabine + S1 (Sakai, 2018);
(6) gemcitabine + capecitabine + oxaliplatin (Markussen, 2020);
(7) gemcitabine + cisplatin + ramucirumab (Valle, 2020);
(8) gemcitabine + cisplatin + merestinib (Valle, 2020);
(9) gemcitabine + oxaliplatin (Ramaswamy, 2017, retrospective cohort study).

The systematic review by Jiang (2021) included eight studies in which gemcitabine + oxaliplatin was used in one of the treatment arms. Direct comparisons were available for the following regimens:

(1) 5-FU + leucovorin (FUFA) (Sharma, 2010);
(2) best supportive care (Sharma, 2010);
(2) capecitabine + oxaliplatin (Kim, 2019);
(3) gemcitabine + oxaliplatin + cetuximab (Malka, 2014; Chen, 2015);
(4) gemcitabine + oxaliplatin + erlotinib (Lee, 2012; Kim, 2015);
(5) 5-FU + cisplatin + radiotherapy (Philip, 2015);
(6) gemcitabine + cisplatin (Ramaswamy, 2017, retrospective cohort study).

A Bayesian network meta-analysis was conducted using a random effects model.
Risk of bias was assessed using the Cochrane reviewer bias risk assessment criteria. Jiang (2021) judged that there was a low risk of bias with regard to blinding of outcome assessment and incomplete outcome data. There was a high risk of bias with regard to blinding of participants and personnel. In several studies, there was an unclear risk of bias for random sequence generation, allocation concealment, selective reporting, and other bias.

Results

Comparison 1: gemcitabine + cisplatin versus other first-line regimens

Overall survival

In the RCT by **Vogel (2018)**, median overall survival was 12.8 months for patients who received gemcitabine + cisplatin + panitumumab and 20.1 months for patients who received gemcitabine + cisplatin. The HR was 0.70 (95%CI 0.41 to 1.18). The difference in weeks fulfills the minimal clinically (patient) relevant difference of > 16 weeks, however the hazard ratio does not fulfill the minimal clinically (patient) relevant difference of HR < 0.7.

In the RCT by **Oh (2022)**, median overall survival was 12.8 months (95%CI 11.1 to 14.0) in patients receiving gemcitabine + cisplatin + durvalumab and 11.5 months (95%CI 10.1 to 12.5) in patients receiving gemcitabine + cisplatin + placebo. This difference was considered not clinically relevant, as the gain in median overall survival was less than 16 weeks and the hazard ratio was > 0.7: HR 0.80 (95%CI: 0.66 to 0.97; p=0.021).

In the RCT by **Kelley (2023)**, the median overall survival was 12.7 months (95%CI 11.5 to 13.6) for patients who received gemcitabine + cisplatin + pembrolizumab and 10.9 months (95%CI 9.9 to 11.6) for patients who received gemcitabine + cisplatin + placebo. This difference was considered not clinically relevant, as the gain in overall survival was less than 16 weeks and the hazard ratio was > 0.7: HR 0.83 (95%CI: 0.72 to 0.95; p=0.034)

In the network meta-analysis by **Jiang (2021)**, overall survival was reported by 23 studies. Table 1 shows outcome data for overall survival, progression-free survival, and toxicity (only clinically relevant differences are shown) between patients who received gemcitabine + cisplatin and patients who received other regimens.

Patients who received gemcitabine + cisplatin showed a clinically relevant <u>longer</u> overall survival (HR< 0.7 or >1.43) compared with:
- best supportive care (indirect comparisons only);
- 5-FU + leucovorin (FUFA) (indirect comparisons only);
- 5-FU + cisplatin + radiotherapy (indirect comparisons only);

Patients who received gemcitabine + cisplatin showed a clinically relevant <u>shorter</u> overall survival (HR<0.7 or >1.43) compared with:
- gemcitabine + sorafenib (indirect comparisons only);

Quality of life

Neither RCTs by Vogel (2018), Oh (2022) and Kelley (2023) nor the systematic review and network meta-analysis by Jiang (2021) provided any data on quality of life.

Progression-free survival

In the RCT by **Vogel (2018)**, median progression-free survival was 6.5 months for patients who received gemcitabine + cisplatin + panitumumab and 8.3 months for patients who received gemcitabine + cisplatin. This difference was considered not clinically relevant as the gain in PFS was shorter than 16 weeks and the hazard ratio was > 0.70: HR 0.73 (95%CI 0.45 to 1.21).

In the RCT by **Oh (2022)**, median progression-free survival was 7.2 months (95%CI 6.7 to 7.4) in patients receiving gemcitabine + cisplatin + durvalumab and 5.7 months (95%CI 5.6 to 6.7) in patients receiving gemcitabine + cisplatin + placebo. This difference was considered not

clinically relevant, as the gain in PFS was shorter than 16 weeks and the hazard ratio was > 0.7: HR 0.75 (95% CI 0.63 to 0.89; p=0.001).

In the RCT by **Kelley (2023)** median progression-free survival was 6.5 months (95%CI 5.7 to 6.9) for patients who received gemcitabine + cisplatin + pembrolizumab and 5.6 months (95%CI 5.1 to 6.6) for patients who received gemcitabine + cisplatin + placebo. This difference was considered not clinically relevant, as the gain in PFS was shorter than 16 weeks and the hazard ratio was > 0.7: HR 0.86 (95%CI: 0.75 to 1.00; p=0.023).

In the network meta-analysis by **Jiang (2021)**, progression-free survival was reported by 23 studies.

Patients who received gemcitabine + cisplatin showed a clinically relevant <u>longer</u> progression-free survival (HR< 0.7 or >1.43) compared with:
- best supportive care (indirect comparisons only);
- S1 (indirect comparisons only);

Patients who received gemcitabine + cisplatin showed a clinically relevant <u>shorter</u> progression-free survival (HR<0.7 or >1.43) compared with:
- gemcitabine + oxaliplatin (direct comparison from retrospective study);
- capecitabine + oxaliplatin (indirect comparisons only);
- 5-FU + oxaliplatin (indirect comparisons only);
- gemcitabine + oxaliplatin + erlotinib (indirect comparisons only);
- gemcitabine + oxaliplatin + cetuximab (indirect comparisons only);
- gemcitabine + sorafenib (indirect comparisons only);

Toxicity

In the RCT by **Vogel (2018)**, the most common grade 3 or 4 events were leucopenia 13/59 (22%) in the gemcitabine, cisplatin and panitumumab group vs. 2/28 (29%) in the gemcitabine and cisplatin group), neutropenia (26/59 [44%] vs. 13/28 [47%]), thrombopenia (18/59 [21%] vs 12/28 [43%]), anemia (7/59 [12%] vs. 3/28 [11%]) and infection (6/59 [10%] vs 6/28 [21%]). In the panitumumab group, grade ≥3 rash was observed in 7/59 patients (12%) and grade ≥3 acne was observed in 10/59 patients (17%). None of these differences were considered clinically relevant.

In the RCT by **Oh (2022)**, 256/338 (75.7%) of patients who received gemcitabine, cisplatin and durvalumab experienced a grade 3 or 4 event, compared with 266/342 (77.8%) of patients who received gemcitabine and cisplatin. The most common grade 3 or 4 events were neutropenia (65/338=19.2% in the intervention group versus 69/342=20.2% in the control group) and anemia (64/338=18.9% in the intervention group versus 64/342=18.7% in the control group). None of these differences were considered clinically relevant.

In the RCT by **Kelley (2023)**) 369/534 (70%) of patients who received gemcitabine, cisplatin and pembrolizumab experienced a grade 3 or 4 event, compared with 367/536 (69%) of patients who received gemcitabine, cisplatin and placebo. The most common grade 3 or 4 events were decreased neutrophil count (grade 3: 167/529 [32%] versus 171/534 [32%], grade 4: 90/529 [17%] versus 82/534 [15%]), anaemia (grade 3: 150/529 [28%] versus 150/534 [28%], grade 4: 2/529 [<1%] versus 4/534 [1%]), decreased platelet count (grade 3: 64/529 [12%] versus 67/534 [13%], grade 4: 30/529 [6%] versus 40/534 [7%]), fatigue (grade 3: 25/529 [5%] versus 22/534 [4%], grade 4: 1/529 [<1%] versus 0/534 [0%]), and decreased

white blood cell count (grade 3: 57/529 [11%] versus 44/534 [8%], grade 4: 4/529 [1%] versus 3/534 [1%]). None of these differences were considered clinically relevant.

For the network meta-analysis by **Jiang (2021)**, only hazard ratios were reported. Based on these data, it is not possible to judge whether any differences are considered clinically relevant.

Level of evidence of the literature

Comparison 1: gemcitabine + cisplatin versus other first-line regimens

The evidence was derived from 1 systematic review of (mainly) RCTs, but with indirect comparisons, and three additional RCTs. Therefore, the level of evidence for all reported outcome measures started at 'high quality'.

Overall survival

Vogel (gemcitabine + cisplatin + panitumumab versus gemcitabine + cisplatin)
The level of evidence regarding the outcome measure overall survival was downgraded by three levels because of study limitations (-1; risk of bias because of a lack of information about randomization and allocation procedures); and number of included patients (-2; imprecision because the 95% confidence interval of the hazard ratio overlaps with the boundary for clinical relevance and this was a single small study.

Oh (gemcitabine + cisplatin + durvalumab versus gemcitabine + cisplatin)
The level of evidence regarding the outcome measure overall survival was downgraded by two levels because the 95% confidence interval of the hazard ratio overlaps with the boundary for clinical relevance and this was a single study (-2; imprecision).

Kelley (gemcitabine + cisplatin + pembrolizumab versus gemcitabine + cisplatin)
The level of evidence regarding the outcome measure overall survival was not downgraded.

Jiang (gemcitabine + cisplatin versus 19 other first-line regimens)
The level of evidence regarding the outcome measure overall survival was downgraded by three levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology); (-1; indirectness because several results were based on indirect comparisons only); and number of included patients (-1; imprecision because the 95% confidence interval of all hazard ratios overlap with the boundary for clinical relevance).

Progression-free survival

Vogel (gemcitabine + cisplatin + panitumumab versus gemcitabine + cisplatin)
The level of evidence regarding the outcome measure progression-free survival was downgraded by three levels because of study limitations (-1; risk of bias because of a lack of information about randomization and allocation procedures); and number of included patients (-2; imprecision because the 95% confidence interval of the hazard ratio overlaps with the boundary for clinical relevance and this was a single small study.

Oh (gemcitabine + cisplatin + durvalumab versus gemcitabine + cisplatin)
The level of evidence regarding the outcome measure progression-free survival was downgraded by two levels because the 95% confidence interval of the hazard ratio overlaps with the boundary for clinical relevance and this was a single study (-2; imprecision).

Kelley (gemcitabine + cisplatin + pembrolizumab versus gemcitabine + cisplatin)
The level of evidence regarding the outcome measure progression-free survival was not downgraded.

Jiang (gemcitabine + cisplatin versus 19 other first-line regimens)

The level of evidence regarding the outcome measure progression-free survival was downgraded by three levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology); (-1; indirectness because several results were based on indirect comparisons only); and number of included patients (-1; imprecision because the 95% confidence interval of all hazard ratios overlap with the boundary for clinical relevance).

Toxicity

Vogel (gemcitabine + cisplatin + panitumumab versus gemcitabine + cisplatin)
The level of evidence regarding the outcome measure toxicity was downgraded by three levels because of study limitations (-1; risk of bias because of a lack of information and randomization and allocation procedures); and number of included patients (-2; imprecision because this was a single study with low numbers of adverse events).

Oh (gemcitabine + cisplatin + durvalumab versus gemcitabine + cisplatin)
The level of evidence regarding the outcome measure toxicity was downgraded by two levels (-2; imprecision because this was a single study with low numbers of adverse events).

Kelley (gemcitabine + cisplatin + pembrolizumab versus gemcitabine + cisplatin)
The level of evidence regarding the outcome measure toxicity was downgraded by one level (-1; imprecision because this was a single study with low numbers of adverse events).

Conclusions

Gemcitabine + cisplatin

Overall survival

Very low GRADE	The evidence is very uncertain about the effect of first-line treatment with gemcitabine + cisplatin + panitumumab on **overall survival** when compared with gemcitabine + cisplatin in patients with a *KRAS* wild-type cholangiocarcinoma or gallbladder carcinoma. *Source: Vogel (2018)*

Low GRADE	The evidence suggests that first-line treatment with gemcitabine + cisplatin + durvalumab does not increase or reduce **overall survival** when compared with gemcitabine + cisplatin in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma. *Source: Oh (2022)*

High GRADE	First-line treatment with gemcitabine + cisplatin + pembrolizumab results in little to no difference in **overall survival** when compared with gemcitabine + cisplatin in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma. *Source: Kelley (2023)*

Very low GRADE	The evidence is very uncertain about the effect of first-line treatment with - best supportive care; - gemcitabine monotherapy; - S1; - 5-FU + leucovorin (FUFA); - gemcitabine + oxaliplatin; - capecitabine + oxaliplatin; - irinotecan + cisplatin; - gemcitabine + S1; - 5-FU + oxaliplatin; - S1 + cisplatin; - gemcitabine + cisplatin + S1; - gemcitabine + capecitabine + oxaliplatin; - gemcitabine + cisplatin + cediranib; - gemcitabine + oxaliplatin + erlotinib; - gemcitabine + oxaliplatin + cetuximab; - gemcitabine + sorafenib; - gemcitabine + cisplatin + ramucirumab; - gemcitabine + cisplatin + merestinib; - 5-FU + cisplatin + radiotherapy; on **overall survival** when compared with gemcitabine + cisplatin in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma *Source: Jiang (2021)*

Quality of life

No GRADE	No evidence was found regarding the effect of first-line treatment with gemcitabine + cisplatin on quality of life when compared with other first-line treatment regimens in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma. *Source*: -

Progression-free survival

Very low GRADE	The evidence is very uncertain about the effect of first-line treatment with gemcitabine + cisplatin + panitumumab on **progression-free survival** when compared with gemcitabine + cisplatin in patients with a KRAS wild-type cholangiocarcinoma or gallbladder carcinoma. *Source: Vogel (2018)*

Progression-free survival

Low GRADE	The evidence suggests that first-line treatment with gemcitabine + cisplatin + panitumumab does not increase or reduce **progression-free survival** when compared with gemcitabine + cisplatin in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma. *Source: Oh (2022)*

Progression-free survival

High GRADE	First-line treatment with gemcitabine + cisplatin + pembrolizumab does not increase or reduce **progression-free survival** when compared with gemcitabine + cisplatin in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma. *Source: Kelley (2023)*

Progression-free survival

Very low GRADE	The evidence is very uncertain about the effect of first-line treatment with - best supportive care; - gemcitabine monotherapy; - S1; - 5-FU + leucovorin (FUFA); - gemcitabine + oxaliplatin; - capecitabine + oxaliplatin; - irinotecan + cisplatin; - gemcitabine + S1; - 5-FU + oxaliplatin; - S1 + cisplatin; - gemcitabine + cisplatin + S1; - gemcitabine + capecitabine + oxaliplatin; - gemcitabine + cisplatin + cediranib; - gemcitabine + oxaliplatin + erlotinib; - gemcitabine + oxaliplatin + cetuximab; - gemcitabine + sorafenib; - gemcitabine + cisplatin + ramucirumab; - gemcitabine + cisplatin + merestinib; - 5-FU + cisplatin + radiotherapy; on **progression-free survival** when compared with gemcitabine + cisplatin in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma *Source: Jiang (2021)*

Toxicity (grade ≥3)

Very low GRADE	The evidence is very uncertain about the effect of first-line treatment with gemcitabine + cisplatin + panitumumab on **toxicity** when compared with gemcitabine + cisplatin in patients with a KRAS wild-type cholangiocarcinoma or gallbladder carcinoma. *Source: Vogel (2018)*

Toxicity (grade ≥3)

Low GRADE	The evidence suggests that first-line treatment with gemcitabine + cisplatin + panitumumab does not reduce or increase **toxicity** when compared with gemcitabine + cisplatin in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma. *Source: Oh (2022)*

Toxicity (grade ≥3)

Moderate GRADE	First-line treatment with gemcitabine + cisplatin + pembrolizumab likely does not reduce or increase **toxicity** when compared with gemcitabine + cisplatin in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma. *Source: Kelley (2023)*

Comparison 2: gemcitabine + oxaliplatin versus other first-line regimens

Overall survival

In the RCT by **Leone (2016)**, median overall survival was 9.9 months (95%CI 5.4 to 14.3) in patients receiving gemcitabine + oxaliplatin + panitumumab and 10.2 months (95%CI 6.4 to 13.9) in patients receiving gemcitabine + oxaliplatin. This difference was considered not clinically relevant, as the gain in median overall survival was less than 16 weeks and the hazard ratio was > 0.7: HR 0.83 (95% CI 0.53 to 1.3; p=0.42).

In the network meta-analysis by **Jiang (2021)**, overall survival was reported by 23 studies.

Patients who received gemcitabine + oxaliplatin showed a clinically relevant longer overall survival (HR< 0.7 or > 1.43) compared with:
- best supportive care (direct comparison from one RCT);
- 5-FU + leucovorin (FUFA) (direct comparison from one RCT);
- 5-FU + cisplatin + radiotherapy (direct comparison from one RCT);

Patients who received gemcitabine + oxaliplatin showed a clinically relevant shorter overall survival (HR<0.7 or >1.43) compared with:
- gemcitabine monotherapy (indirect comparisons only);
- gemcitabine + S1 (indirect comparisons only);
- S1 + cisplatin (indirect comparisons only);
- gemcitabine + cisplatin + S1 (indirect comparisons only);
- gemcitabine + sorafenib (indirect comparisons only).

Quality of life

Neither the RCT by Leone (2016) nor the systematic review and network meta-analysis by Jiang (2021) provided any data on quality of life.

Progression-free survival

In the RCT by **Leone (2016)**, median progression-free survival was 5.3 months (95%CI 3.3 to 7.2) in patients receiving gemcitabine + oxaliplatin + panitumumab and 4.4 months (95%CI 2.6 to 6.2) in patients receiving gemcitabine + oxaliplatin. This difference was considered not clinically relevant, as the gain in PFS was shorter than 16 weeks and the hazard ratio was > 0.7: HR 0.78 (95% CI 0.51 to 1.21; p=0.27).

In the network meta-analysis by **Jiang (2021)**, progression-free survival was reported by 23 studies. Table 2 shows the outcomes with a clinically relevant difference between patients who received gemcitabine + oxaliplatin and patients who received other regimens.

Patients who received gemcitabine + oxaliplatin showed a clinically relevant longer progression-free survival (HR < 0.7 or > 1.43) compared with:
- best supportive care (direct comparison from one RCT);
- gemcitabine monotherapy (indirect comparisons only);
- S1 (indirect comparisons only);
- 5-FU + leucovorin (FUFA) (direct comparison from one RCT);
- gemcitabine + cisplatin (direct comparison from retrospective study);
- irinotecan + cisplatin (indirect comparisons only);

- gemcitabine + S1 (indirect comparisons only);
- S1 + cisplatin (indirect comparisons only);
- gemcitabine + cisplatin + S1 (indirect comparisons only);
- gemcitabine + capecitabine + oxaliplatin (indirect comparisons only);
- gemcitabine + cisplatin + cediranib; (indirect comparisons only);
- gemcitabine + cisplatin + ramucirumab (indirect comparisons only);
- gemcitabine + cisplatin + merestinib (indirect comparisons only);
- 5-FU + cisplatin + radiotherapy (direct comparison from one RCT).

Toxicity

In the RCT by **Leone (2016)**, the most frequently observed grade ≥3 events included cholestasis/hepatic toxicity (9/45=20% in the intervention group and 6/44=14% in the control group), skin toxicity (6/45=13% in the intervention group and 1/44=2% in the control group), diarrhea (6/45=13% in the intervention group and 3/44=7% in the control group), asthenia (5/45=11% in the intervention group and 3/44=7% in the control group), and nausea (4/45=9% in the intervention group and 2/44=5% in the control group). None of these differences were considered clinically relevant.

For the network meta-analysis by **Jiang (2021)**, only hazard ratios were reported. Based on these data, it is not possible to judge whether any differences are considered clinically relevant.

Level of evidence of the literature

Comparison 2: gemcitabine + oxaliplatin versus other first-line regimens

The evidence was derived from 1 systematic review of (mainly) RCTs and one additional RCT. Therefore, the level of evidence for all reported outcome measures started at 'high quality'.

Overall survival

Leone (gemcitabine + oxaliplatin + panitumumab versus gemcitabine + oxaliplatin)
The level of evidence regarding the outcome measure overall survival was downgraded by two levels because the 95% confidence interval of the hazard ratio overlaps with the boundary for clinical relevance and this was a single small study (-2; imprecision).

Jiang (gemcitabine + oxaliplatin versus 19 other first-line regimens)
The level of evidence regarding the outcome measure overall survival was downgraded by three levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology); (-1; indirectness because several results were based on indirect comparisons only); and number of included patients (-1; imprecision because the 95% confidence interval of all hazard ratios overlap with the boundary for clinical relevance).

Progression-free survival

Leone (gemcitabine + oxaliplatin + panitumumab versus gemcitabine + oxaliplatin)
The level of evidence regarding the outcome measure progression-free survival was downgraded by two levels because the 95% confidence interval of the hazard ratio overlaps with the boundary for clinical relevance and this was a single small study (-2; imprecision).

Jiang (gemcitabine + oxaliplatin versus 19 other first-line regimens)
The level of evidence regarding the outcome measure progression-free survival was downgraded by three levels because of study limitations (-1; risk of bias because of incomplete reporting of study methodology); (-1; indirectness because several results were based on indirect comparisons only); and number of included patients (-1; imprecision because the 95% confidence intervals of most hazard ratios overlap with the boundary for clinical relevance).

Toxicity

Leone (gemcitabine + oxaliplatin + panitumumab versus gemcitabine + oxaliplatin)
The level of evidence regarding the outcome measure toxicity was downgraded by two levels because this was a single small study (-2; imprecision).

Overall survival

Low GRADE	The evidence suggests that first-line treatment with gemcitabine + oxaliplatin + panitumumab does not increase or reduce **overall survival** when compared with gemcitabine + oxaliplatin in patients with a non-resectable, locally advanced or metastasized KRAS wild-type cholangiocarcinoma or gallbladder carcinoma. *Source: Leone (2016)*

Very low GRADE	The evidence is very uncertain about the effect of first-line treatment with - best supportive care; - gemcitabine monotherapy; - S1; - 5-FU + leucovorin (FUFA); - gemcitabine + cisplatin; - capecitabine + oxaliplatin; - irinotecan + cisplatin; - gemcitabine + S1; - 5-FU + oxaliplatin; - S1 + cisplatin; - gemcitabine + cisplatin + S1; - gemcitabine + capecitabine + oxaliplatin; - gemcitabine + cisplatin + cediranib; - gemcitabine + oxaliplatin + erlotinib; - gemcitabine + oxaliplatin + cetuximab; - gemcitabine + sorafenib; - gemcitabine + cisplatin + ramucirumab; - gemcitabine + cisplatin + merestinib; - 5-FU + cisplatin + radiotherapy; on **overall survival** when compared with gemcitabine + oxaliplatin in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma *Source: Jiang (2021)*

Quality of life

No GRADE	No evidence was found regarding the effect of first-line treatment with gemcitabine + oxaliplatin on **quality of life** when compared with other first-line treatment regimens in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma. *Source: -*

Progression-free survival

Low GRADE	The evidence suggests that first-line treatment with gemcitabine + oxaliplatin + panitumumab does not increase or reduce **progression-free survival** when compared with gemcitabine + oxaliplatin in patients with a non-resectable, locally advanced or metastasized KRAS wild-type cholangiocarcinoma or gallbladder carcinoma.

	Source: Leone (2016)

Very low GRADE	The evidence is very uncertain about the effect of first-line treatment with - best supportive care; - gemcitabine monotherapy; - S1; - 5-FU + leucovorin (FUFA); - gemcitabine + cisplatin; - capecitabine + oxaliplatin; - irinotecan + cisplatin; - gemcitabine + S1; - 5-FU + oxaliplatin; - S1 + cisplatin; - gemcitabine + cisplatin + S1; - gemcitabine + capecitabine + oxaliplatin; - gemcitabine + cisplatin + cediranib; - gemcitabine + oxaliplatin + erlotinib; - gemcitabine + oxaliplatin + cetuximab; - gemcitabine + sorafenib; - gemcitabine + cisplatin + ramucirumab; - gemcitabine + cisplatin + merestinib; - 5-FU + cisplatin + radiotherapy; on **progression-free survival** when compared with gemcitabine + oxaliplatin in patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma *Source: Jiang (2021)*

Toxicity (grade ≥3)

Low GRADE	The evidence suggests that first-line treatment with gemcitabine + oxaliplatin + panitumumab does not increase or reduce **toxicity** when compared with gemcitabine + oxaliplatin in patients with a non-resectable, locally advanced or metastasized KRAS wild-type cholangiocarcinoma or gallbladder carcinoma. *Source: Leone (2016)*

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

Sinds de publicatie van de ABC-02 studie (Valle, 2010) is er geen effectievere behandeling dan gemcitabine + cisplatin gevonden die voldoet aan de gestelde definitie van klinisch relevante overlevingswinst (een verschil van >12 weken of HR < 0,70).

De systematische search leverde vier RCT's op waarin directe vergelijkingen tussen gemcitabine + cisplatin of gemcitabine + oxaliplatin versus andere eerstelijns behandelopties werden gemaakt (Vogel, 2018, PICCA studie; Oh, 2022, TOPAZ-1 trial; Kelley, 2023, KEYNOTE-966 trial; Leone, 2016, Vecti-BIL study). Daarnaast werd een netwerk meta-analyse geïncludeerd (Jiang, 2021) waarin de effectiviteit en veiligheid van 20 verschillende eerstelijns behandelopties werd onderzocht. Er werden in de netwerk meta-analyse voornamelijk indirecte vergelijkingen gemaakt. In de overwegingen heeft de werkgroep zich voornamelijk gebaseerd op de RCT's waarin directe vergelijkingen werden gemaakt. Er is gekeken naar de vergelijkingen van gemcitabin + cisplatin versus andere regimes (vergelijking 1) en gemcitabine + oxaliplatin versus andere regimes (vergelijking 2).

Naast de eerdergenoemde landmarkstudie van Valle (2010) zijn recent twee relevante RCT's gepubliceerd te weten gemcitabine + cisplatin + durvalumab versus gemcitabine + cisplatin + placebo (Oh, 2022, TOPAZ-1 trial) en gemcitabine + cisplatin + pembrolizumab versus gemcitabine + cisplatin (Kelley, 2023, KEYNOTE-966 trial). Voor beide studies geldt dat de studies wel een statistisch significante absolute winst in mediane OS toonden, respectievelijk 1,3 en 1,8 maanden, maar dat deze winst volgens de beroepsgroep als onvoldoende klinisch relevant wordt beoordeeld (PASKWIL criteria). Naar analogie bij andere tumortypen is de verwachting dat er in de toekomst subgroepen geïdentificeerd zullen worden die meer baat hebben bij de toevoeging van durvalumab dan wel pembrolizumab aan gemcitabine + cisplatin.
Voor graad 3-4 toxiciteit werden in de RCT's geen klinisch relevante verschillen gevonden.
Voor kwaliteit van leven werden geen data gerapporteerd

In de netwerk meta-analyse werden klinisch relevante verschillen in overleving ten gunste van gemcitabine + cisplatin gevonden vergeleken met: (1) best supportive care; (2) 5-FU + leucovorin (FUFA); en (3) 5-FU + cisplatin + radiotherapie. Een verschil in het nadeel van gemcitabine + cisplatin werd gevonden in vergelijking met gemcitabine + sorafenib. De werkgroep adviseert deze laatste combinatie niet, omdat dit verschil gebaseerd was op indirecte vergelijkingen tussen behandelopties en de bewijskracht daarom zeer laag is.
Voor graad 3-4 toxiciteit werden geen klinisch relevante verschillen gevonden (zeer lage tot redelijke bewijskracht). Voor kwaliteit van leven werden geen data gerapporteerd.

In tegenstelling tot gemcitabine + cisplatin is er geen gerandomiseerde fase 3 studie verricht met gemcitabine + oxaliplatin. Deze combinatie van middelen wordt buiten Europa wel vaak toegepast. De werkgroep adviseert de combinatie gemcitabine + oxaliplatin niet als standaard zorg. Omdat voor toediening van cisplatin een behouden nierfunctie nodig is, is het bij patiënten met een verminderde nierfunctie (egfr< 50 ml/min) een optie om cisplatin door oxaliplatin te vervangen of alleen gemcitabine monotherapie te geven. Helaas is er geen RCT verricht die gemcitabine + oxaliplatin met gemcitabine monotherapie vergeleken heeft. Er is daarom geen uitspraak te doen welk regimen (gemcitabine + oxaliplatin of gemcitabine monotherapie) de voorkeur heeft bij een onvoldoende nierfunctie.

Bij patiënten met een hyperbilirubinemie veroorzaakt door galwegobstructie waarbij ondanks adequate drainage het bilirubine niet genormaliseerd is, kan wel gemcitabine + cisplatin gestart worden (Lamarca, 2015).

Omdat het mediane aantal cycli gemcitabine + cisplatin in de landmark studie (Valle, 2010) acht cycli was en er onvoldoende bewijslijst is om langer dan 6 maanden te behandelen, is het advies na 6 maanden behandeling met gemcitabine + cisplatin te pauzeren. Bij progressie> 3 maanden na staken van gemcitabine + cisplatin en eerdere goede tolerantie, kan overwogen worden gemcitabine + cisplatin te herintroduceren. Indien er sprake is van gecombineerde histologie van galweg/galblaascarcinoom en hepatocellulair carcinoom (HCC), wordt de keuze van systeemtherapie bepaald op basis van de histologie die het meest prominent aanwezig is, of op basis van tumormarkerdominantie (Alfa FP en Ca 19.9). Omdat de geïncludeerde studies ook patiënten met lokaal gevorderde tumoren bevatten, zijn deze aanbevelingen ook in deze situatie van toepassing.

Aantonen maligniteit

Voor de start van systemische behandeling is het nodig om weefsel van de tumor te verkrijgen om de diagnose van kanker te bevestigen. Bij alle patiënten met galweg- of galblaascarcinoom is er vaak sprake van afstandsmetastasen bij presentatie. Vooral peritoneale en lever metastasen zijn geschikt voor een percutaan biopt. Bij iCCA is een percutaan biopt van de primaire tumor een goed alternatief, omdat er meestal sprake is van 1 of meer grote tumoren in de lever.

Bij perihilair cholangiocarcinoom (pCCA) en distaal cholangiocarcinoom (dCCA) is er sprake van (kleine) tumoren in de extrahepatische galweg. Vaak is op CT zelfs geen tumor zichtbaar en slechts een strictuur of abrupte stop van de galwegen. Een percutaan biopt is dan niet zinvol. In de praktijk is de standaard om bij patiënten met pCCA en dCCA de tumor cytologisch te benaderen middels een galgangbrush ten tijde van de galwegdrainage. De sensitiviteit (35-60%), specificiteit (89-100%), positive predictive value (59%) and negative predictive value (89-100%) van galwegcytologie is echter niet optimaal (Hacihasanoglu, 2018; Ponsioen, 199). Nieuwe technieken worden onderzocht voor het verkrijgen van histologie (Laquière, 2020; Wen, 2020). Echter, een zekere diagnose van dysplasie of maligniteit in galgang brushes is vaak lastig door overlappende kenmerken met reactieve atypie door ontsteking bij PSC, stenen en stent. Vanaf 1 januari 2024 is vanuit de NVVP besloten tot een gestandaardiseerde benadering van pancreas- en galwegcytologie en biopten conform WHO “Reporting System for Pancreaticobiliary Cytopathology” (IAC-IARC-WHO, 2022; Pitman, 2023) in plaats van de classificatie volgens Papanicolaou Society of Cytopathology (PSC) Systeem uit 2015 (Pitman, 2015).

Bij twijfel aan de diagnose maligniteit op basis van de morfologie, kan moleculair onderzoek helpen om, in geval van pathogene mutaties, de diagnose van galwegcarcinoom te bevestigen. Next generation sequencing (NGS) kan worden verricht op paraffine gefixeerd materiaal dan wel op cytologisch bewerkt materiaal (Giemsa weefselglaasjes). Ook kunnen aanvullende immunohistochemische kleuringen op paraffine materiaal worden verricht (bv. P53, NTRK, MMR eiwitten, Her-2) (Hilburn, 2022; Macias, 2022; Vogel, 2023).

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

Doelen van patiënten kunnen zijn vergroten van overleving, verbetering/behoud van kwaliteit van leven. Deze voorkeuren zijn heel persoonlijk en dienen geëxploreerd te worden in een gezamenlijk gesprek. Eventuele voordelen van de behandeling met palliatieve systeemtherapie kunnen zijn langer leven en minder klachten ervaren indien de tumor door

de behandeling kleiner wordt. Maar nadelen kunnen de bijwerkingen van de chemotherapie zijn die een negatief effect op de kwaliteit van leven kunnen geven en de belasting van de frequente gang naar het ziekenhuis met bijbehorende afspraken voor onderzoeken, gesprekken en behandelingen. Door middel van Samen Beslissen kan tot een keuze worden gekomen om wel of niet te starten met palliatieve systeemtherapie. Helaas is het van tevoren niet te voorspellen wat het effect van de behandeling op de tumor zal zijn. Wel is van de gerandomiseerde studie (Valle, 2010) bekend dat bij gemcitabine + cisplatin op de 1e CT evaluatie bij 80% van de patiënten stabiele ziekte en respons toonde. Het is bekend dat de response rate bij gemcitabine + cisplatin het hoogste is voor de groep met galblaastumoren in vergelijking met de galwegtumoren. Naast data uit gerandomiseerde studies kunnen ook gegevens over effectiviteit besproken worden aan de hand van data uit de dagelijkse praktijk. NKR data tonen bij patiënten die starten met palliatieve systeemtherapie een 1 jaarsoverleving van 34% (perihilair galwegcarcinoom 43%, galblaas 22%) (NKR 2017-2021). In geval van best supportive care is de mediane overleving 1.5-3 maanden (NKR 2017-2021). Dit zijn allemaal gegevens die betrekking hebben op de hele groep, maar niet op de individuele patiënt.

Kosten (middelenbeslag)
De chemotherapie is uit patent en is daarmee geen dure behandeling. Echter, er zijn ook kosten voor de dagbehandeling en bijbehorende onderzoeken en gesprekken met zorgverleners.

Aanvaardbaarheid, haalbaarheid en implementatie
Alleen gemcitabine + cisplatin, gemcitabine + oxaliplatin, en gemcitabine monotherapie zijn te overwegen in de eerste lijn. Andere behandelingen zijn ineffectief, alleen indirect vergeleken, óf voldoen niet aan de Nederlandse criteria voor voldoende effectiviteit. De aanbevelingen zijn in overeenstemming met de huidige zorg.

Aanbeveling

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

Geef bij patiënten die in aanmerking komen voor palliatieve systemische therapie gemcitabine + cisplatin.

Geef ook gemcitabine + cisplatin bij geconjungeerde hyperbilirubine op basis van galwegobstructie; bij goede drainage is het niet nodig te wachten op normaliseren van het bilirubine.

Overweeg in geval van een contra-indicatie voor cisplatin, substitutie door oxaliplatin of geef gemcitabine monotherapie.

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Bijlagen bij module 11 Palliatieve systemische behandeling in de 1e lijn

Evidence tables

Evidence table for systematic reviews of RCTs and observational studies

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison/control (C)	Follow-up	Outcome measures and effect size	Comments
Jiang (2021)	Type of study: Systematic review and network meta-analysis Literature search: PubMed, Embase, and Cochrane Library, up to August 10, 2020 Included studies: **A:** Sharma (2010) **B:** Kim (2019) **C:** Valle (2015) **D:** Valle (2010) **E:** Dos Santos (2020) **F:** Huang (2015) **G:** Morizane (2019) **H:** Li (2016) **I:** Schinzari (2017) **J:** Okusaka (2010) **K:** Malka (2014) **L:** Lee (2012) **M:** Phelip (2015) **N:** Moehler (2014) **O:** Chen (2015) **P:** Novarino (2013) **Q:** Sasaki (2013)	Inclusion criteria: • study type: published RCT of II/III period • subjects: advanced biliary tract cancer confirmed by histology • patients with advanced BTC receiving first-line chemotherapy • primary outcome indicators: reported progression-free survival, overall survival, and objective remission rate • secondary outcome indicators: adverse events (neutropenia grade ≥ 3, vomiting,	**A:** I1: best supportive care; I2: fluorouracil (425 mg/m^2 bolus infusion weekly for 30 wks) + folinic acid (20 mg/^{2} bolus infusion weekly for 30 wks) **B:** capecitabine (1000 mg/m^2 p.o. b.i.d. on day 1-14) + oxaliplatin (130 mg/m^2 infused over 120 min on day 1) **C:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks) + cisplatin (25 mg/m^2 on day 1 and 8 every 3 wks) + cediranib (20 mg p.o. q.d.) **D:** gemcitabine (1000 mg/m^2 i.v. on day 1, 8 and 15 every 4 wks for 6 cycles) **E:** irinotecan (65 mg/m^2 i.v. on day 1 and 8 every 3 wks) + cisplatin (60 mg/m^2 i.v. on day 1 every 3 wks) **F:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 15 every 4 wks) + S-1 (80-	**A:** gemcitabine (900 mg/m^2 i.v. on day 1 and 8 every 3 wks for a maxmium of 6 cycles) + oxaliplatin (80 mg/m^2 i.v. on day 1 and 8 every 3 wks for a maxmium of 6 cycles) **B:** gemcitabine (1000 mg/m^2 infused over 100 min on day 1 and 8) + oxaliplatin (100 mg/m^2 infused over 120 min on day 1) **C:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 21 days) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 3 wks) + placebo **D:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 21 days) **E:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks) + cisplatin (60 mg/m^2 i.v. on day 1 every 3 wks) **F:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 8	Length of follow-up: Not reported. Loss to follow-up or missing outcome data: Not reported.	Overall survival Months, median **A:** I1/I2/C: 4.5/4.6/9.5 **B:** I/C: 10.6/10.4 **C:** I/C: 14.1/11.9 **D:** I/C: 8.1/11.7 **E:** I/C: 11.9/9.8 **F:** I/C: 8.2/10.2 **G:** I/C: 15.1/13.4 **H:** I/C1/C2: 11/10/6 **I:** I/C: 13/7.5 **J:** I/C: 7.7/11.2 **K:** I/C: 11/12.4 **L:** I/C: 9.5/9.5 **M:** I/C: 13.5/19.9 **N:** I/C: 8.4/11.2 **O:** I/C: 10.6/9.8 **P:** I/C: 14.1/8.3 **Q:** I/C: 8.9/9.2 **R:** I/C: 12.5/9 **S:** I/C: 9.9/10.1 **T:** I/C: 13.5/12.6 **U:** I/C: 8.7/12 **V:** I/C: 10.2/8 **W:** I1/I2/C1+C2: 10.45/14.03/13.04 **X:** I/C: 7.79/8.02 See Tables 1 and 2 for hazard ratios	Abbreviations: BSC = best supportive care FUFA = fluorouracil + folinic acid GEMOX = gemcitabine + oxaliplatin GP = gemcitabine + cisplatin XELOX = capecitabine + oxaliplatin Review authors' conclusion: This network meta-analysis demonstrated that chemotherapy combined with targeted therapy has better efficacy and lower incidence of adverse events than chemotherapy alone.

	R: Morizane (2013) **S:** Kang (2012) **T:** Sakai (2018) **U:** Markussen (2020) **V:** Kim (2015) **W:** Valle (2020) **X:** Ramaswamy (2017) <u>Study design:</u> **A:** single-center, open-label, randomized trial **B:** multicenter, open-label, randomized phase III trial **C:** multicenter, randomized double-blind, placebo-controlled phase II trial **D:** multicenter, open-label, randomized phase III trial **E:** single-center, open-label, randomized phase II trial **F:** randomized trial **G:** multicenter, open-label, randomized phase III trial **H:** single-center, open-label, randomized trial	diarrhea, and fatigue) <u>Exclusion criteria:</u> • studies in which patients were treated with cisplatin-based double or multiple concurrent agents • letters, reviews, case reports, non-human studies, and articles that do not provide raw data • non-English articles • non-randomized controlled single-arm studies • research includes a comparison of chemotherapy with adjuvant or neoadjuvant treatment • studies that only included patients with specific gene mutations <u>N total at baseline:</u>	120 mg/m^2 p.o. b.i.d. on day 1-14 every 4 wks) **G:** gemcitabine (1000 mg/m^2 i.v. on day 1, 8 and 15 every 3 wks) + S-1 (80-100 mg/m^2 p.o. b.i.d. on day 1-14 every 3 wks) **H:** gemcitabine (1000 mg/m^2 infused over 30 min on day 1 and 15 every 4 wks) + S-1 (80-120 mg/m^2 p.o. b.i.d. on day 1-14 every 4 wks) **I:** leucovorin (100 mg/m^2 infused over 2 hrs on day 1 and 2 every 2 wks) + 5-fluorouracil (400 mg/m^2 bolus infusion on day 1 and 2 and 1200 mg/m^2 infused over 46 hrs every 2 wks) + oxaliplatin (85 mg/m^2 infused over 2 hrs min on day 1 every 2 wks) **J:** gemcitabine (1000 mg/m^2 i.v. on day 1, 8 and 15 every 4 wks) **K:** gemcitabine (1000 mg/m^2 infused over 100 min on day 1 every 2 wks) + oxaliplatin (100 mg/m^2 infused over 120 min on day 2 every 2 wks) + cetuximab (500 mg/m^2 infused over 150 min on day 1 or 2 every 2 wks) **L:** gemcitabine (1000 mg/m^2 infused over 100 min on day 1 every 2 wks) + oxaliplatin (100 mg/m^2 infused over 120 min on day 2 every 2 wks) +	every 3 wks) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 3 wks) **G:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 3 wks) **H:** <u>C1:</u> gemcitabine (1000 mg/m^2 infused over 30 min on day 1, 8 and 15 every 4 wks); <u>C2:</u> S-1 (80-120 mg/m^2 p.o. b.i.d. on day 1-14 every 4 wks) **I:** leucovorin (100 mg/m^2 infused over 2 hrs on day 1 and 2 every 2 wks) + 5-fluorouracil (400 mg/m^2 bolus infusion on day 1 and 2 and 1200 mg/m^2 infused over 46 hrs every 2 wks) **J:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 3 wks) **K:** gemcitabine (1000 mg/m^2 infused over 100 min on day 1 every 2 wks) + oxaliplatin (100 mg/m^2 infused over 120 min on day 2 every 2 wks) **L:** gemcitabine (1000 mg/m^2 infused over 100 min on day 1 every 2 wks) + oxaliplatin (100 mg/m^2 infused over 120 min on day 2 every 2 wks) **M:** gemcitabine (1000 mg/m^2 infused over 100 min on day 1 every 2 wks		<u>Progression-free survival</u> Months, median **A:** I1/I2/C: 2.8/3.5/8.5 **B:** I/C: 5.8/5.3 **C:** I/C: 8/7.4 **D:** I/C: 5/8 **E:** I/C: 5.3/7.8 **F:** I/C: 5.6/6.5 **G:** I/C: 6.8/5.8 **H:** I/C1/C2: 4.9/3.7/1.6 **I:** I/C: 5.2/2.8 **J:** I/C: 3.7/5.8 **K:** I/C: 6.1/5.5 **L:** I/C: 5.8/4.2 **M:** I/C: 5.8/11 **N:** I/C: 3/4.9 **O:** I/C: 6.7/4.1 **P:** I/C: 5.4/3.9 **Q:** I/C: 5.6/4.3 **R:** I/C: 7.15/4.2 **S:** I/C: 5.4/5.7 **T:** I/C: 7.4/5.5 **U:** I/C: 5.7/7.3 **V:** I/C: 6.1/3 **W:** I1/I2/C1+C2: 6.47/6.97/6.64 **X:** not reported See Tables 1 and 2 for hazard ratios **Safety** <u>Neutropenia grade ≥ 3</u> n/N (%) **A:** I1/I2/C: I: N.A./ 2/28 (7%)/ 10/26 (38%) **B:** I/C: 5/106 (5%)/ 16/110 (15%) **C:** I/C: 26/62 (42%)/ 23/62 (37%) **D:** I/C: 33/199 (17%)/ 50/198 (25%)	

	I: randomized phase II trial **J:** multicenter, randomized phase II trial **K:** multicenter, open-label, randomized phase II trial **L:** multicenter, open-label, randomized phase III trial **M:** multicenter, open-label, randomized phase II trial **N:** multicenter, randomized, double-blind, placebo-controlled phase II trial **O:** multicenter, open-label, randomized phase II trial **P:** retrospective cohort study **Q:** multicenter, open-label, randomized phase II trial **R:** multicenter, open-label, randomized phase II trial **S:** single-center, open-label, randomized phase II trial	**A:** I1/I2/C: N = 27/28/27 **B:** I/C: N = 108/114 **C:** I/C: N = 62/62 **D:** I/C: N = 206/204 **E:** I/C: N = 24/23 **F:** I/C: N = 32/34 **G:** I/C: N = 179/175 **H:** I/C1/C2: N = 25/25/25 **I:** I/C: N = 25/23 **J:** I/C: N = 42/41 **K:** I/C: N = 76/74 **L:** I/C: N = 135/133 **M:** I/C: N = 18/16 **N:** I/C: N = 52/50 **O:** I/C: N = 62/60 **P:** I/C: N = 22/18 **Q:** I/C: N = 30/32 **R:** I/C: N = 51/50 **S:** I/C: N = 47/49 **T:** Randomized: N = 246 **U:** I/C: N = 50/50 **V:** I/C: N = 49/54 **W:** I1/I2/C1+C2: N = 106/102/101 **X:** I/C: N = 163/163 <u>Important characteristics:</u> Age, median, years: **A:** I1/I2/C: 51/47/49 **B:** I/C: 62/64 **C:** I/C: 68/65	erlotinib (100 mg p.o. q.d. from day 1) **M:** 5-fluorouracil (300 mg/m^2 infused continuously for 5 days/wk for 5 wks) + cisplatin (20 mg/m^2 on day 1-4 and 29-32) + radiotherapy (50 Gy in 25 fractions) **N:** gemcitabine (1000 mg/m2 i.v. on day 1, 8, 15, 29, 36 and 43 of the first cycle and on day 1, 8 and 15 of all subsequent cycles every 4 wks) + sorafenib (400 mg p.o. b.i.d.) **O:** gemcitabine (800 mg/m^2 infused at FDR of 10 mg/m^2 per min every 2 wks) + oxaliplatin (85 mg/m^2 infused over 120 min every 2 wks) + cetuximab (500 mg/m^2 i.v. on day 1 every 2 wks) **P:** oxaliplatin (85 mg/m^2 infused over 1 hr on day 1 every 2 wks) + 5-fluorouracil (400 mg/m^2 bolus infusion on day 1 and 2 and 600 mg/m^2 infused over 22 hrs every on day 1 and 2 every 2 wks) + folinic acid (200 mg/m^2 infused over 2 hr on day 1 and 2 every 2 wks) **Q:** gemcitabine (1000 mg/m^2 infused over 30 min on day 1 and 15 every 4 wks) + S-1 (80-120	for 12 cycles) + oxaliplatin (100 mg/m^2 infused over 120 min starting 1 hr after the end of the gemcitabine infusion every 2 wks for 12 cycles) **N:** gemcitabine (1000 mg/m2 i.v. on day 1, 8, 15, 29, 36 and 43 of the first cycle and on day 1, 8 and 15 of all subsequent cycles every 4 wks) + placebo **O:** gemcitabine (800 mg/m^2 infused at FDR of 10 mg/m^2 per min every 2 wks) + oxaliplatin (85 mg/m^2 infused over 120 min every 2 wks) **P:** gemcitabine (1250 mg/m^2 infused over 30 min on day 1-8 every 3 wks) **Q:** gemcitabine (1000 mg/m^2 infused over 30 min on day 1, 8 and 15 every 4 wks) **R:** S-1 (80-120 mg/m^2 p.o. b.i.d. on day 1-28 every 6 wks) **S:** gemcitabine (1000 mg/m^2 infused at FDR of 10 mg/m^2 on day 1 and 8 every 3 wks) + cisplatin (60 mg/m^2 infused over 90 min on day 1 every 3 wks) **T:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 3 wks) **U:** gemcitabine (1000 mg/m^2 infused over 30		**E:** not reported **F:** I/C: n = 21/20 **G:** I/C: 106/177 (60%)/ 104/171 (61%) **H:** not reported **I:** I/C: 2/25 (8%)/ 1/23 (4%) **J:** I/C: 16/42 (38%)/ 23/41 (56.1%) **K:** I/C: 17/76 (22%)/ 11/68 (16%) **L:** I/C: 3/135 (2%)/ 5/131 (4%) **M:** I/C: 0/17 (0%)/ 4/16 (25%) **N:** I/C: 2/49 (4%)/ 4/48 (8%) **O:** I/C: 11/62 (18%)/ 2/60 (3%) **P:** I/C: 6/22 (27%)/ 5/18 (28%) **Q:** I/C: 10/30 (33%)/ 7/32 (63%) **R:** I/C: 31/51 (61%)/ 2/50 (4%) **S:** I/C: 14/47 (30%)/ 24/49 (49%) **T:** not reported **U:** I/C: 0/47 (0%)/ 21/49 (43%) **V:** not reported **W:** I1/I2/C1+C2: 51/104 (49%)/ 48/102 (47%)/ 33/100 (33%) **X:** I/C: 4/163 (2%)/ 12/163 (7%) See Tables 1 and 2 for hazard ratios	

	T: multicenter, open-label, randomized phase III study **U:** multicenter, open-label, randomized phase II trial **V:** multicenter, open-label, randomized phase III trial **W:** multicenter, randomized, double-blind phase II trial **X:** retrospective match pair analysis <u>Setting and country:</u> **A:** 1 cancer hospital in India **B:** 10 tertiary hospitals in South Korea **C:** hepatobiliary oncology referral centers in the UK **D:** 37 centers in the UK **E:** 1 cancer hospital in Brazil **F:** China **G:** 33 institutions in Japan **H:** 1 tertiary hospital in China **I:** Italy **J:** 9 study centers in Japan	**D:** I/C: 63/64 **E:** not reported **F:** not reported **G:** I/C: 67/67 **H:** I/C1/C2: 57/55/57 **I:** I/C: 62/61 **J:** I/C: 66/65 **K:** I/C: 61/62 **L:** I/C: 59/61 **M:** I/C: 69/75 **N:** I/C: 64/65 **O:** I/C: 61/59 **P:** I/C: 62/65 **Q:** I/C: 68/75 **R:** I/C: 66/63 **S:** I/C: 60/59 **T:** not reported **U:** I/C: 65/65 **V:** I/C: 59/62 **W:** not reported **X:** I/C: 52/52 Sex, n/N (%) male: **A:** I1/I2/C: I: 6/27 (22%)/ 5/28 (18%)/ 5/26 (19%) **B:** I/C: 74/108 (69%)/ 70/114 (61%) **C:** I/C: 34/62 (55%)/ 28/62 (45%) **D:** I/C: 98/206 (48%)/ 96/204 (47%) **E:** not reported **F:** I/C: 19/32 (59%)/ 22/34 (65%)	mg/m^2 p.o. b.i.d. on day 1-14 every 4 wks) **R:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks) + S-1 (60-100 mg/m^2 p.o. b.i.d. on day 1-14 every 3 wks) **S:** S-1 (80-120 mg/m^2 p.o. b.i.d. on day 1-14 every 3 wks) + cisplatin (60 mg/m^2 infused over 90 min on day 1 every 3 wks) **T:** gemcitabine (1000 mg/m^2 i.v. on day 1 every 2 wks) + cisplatin (25 mg/m^2 i.v. on day 1 every 2 wks) + S-1 (80 mg/m^2 p.o. q.d. on day 1-7 every 2 wks) **U:** gemcitabine (1000 mg/m^2 infused over 30 min every 2 wks) + oxaliplatin (50 mg/m^2 infused over 30 min every 2 wks) + capecitabine (650 mg/m^2 p.o. b.i.d. on day 1-14) **V:** gemcitabine (1000 mg/m^2 infused over 100 min 1 every 2 wks) + oxaliplatin (100 mg/m^2 infused over 120 min every 2 wks) + erlotinib (100 mg p.o. q.d.) **W:** <u>I1:</u> gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks for a maximum of 8 cycles) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 3 wks for a maximum of 8 cycles) + ramucirumab (8	min on day 1 and 8 every 3 wks) + cisplatin (25 mg/m^2 infused over 60 min on day 1 and 8 every 3 wks) **V:** gemcitabine (1000 mg/m^2 infused over 100 min every 2 wks) + oxaliplatin (100 mg/m^2 infused over 120 min every 2 wks) **W:** <u>C1:</u> gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks for a maximum of 8 cycles) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 3 wks for a maximum of 8 cycles) + placebo (i.v.); <u>C2:</u> gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks for a maximum of 8 cycles) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 3 wks for a maximum of 8 cycles) + placebo (p.o. q.d.) **X:** gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 3 wks)			

	K: university hospitals and cancer centers in France and Germany **L:** 11 tertiary hospitals in South Korea **M:** 12 hospitals in France **N:** 11 hospital in Germany **O:** 12 hospital in Tawain **P:** 1 university hospital in Italy **Q:** 12 hospitals in Japan **R:** 19 hospitals in Japan **S:** 1 university hospital in South Korea **T:** 39 institutions in Japan **U:** 2 hospitals in Denmark **V:** 11 tertiary hospitals in South Korea **W:** 81 hospitals in 18 countries (USA, Taiwan, South Korea, Turkey, Argentina, France, Russia, Spain, UK, Germany, Australia, Belgium, Hungary, Czech Republic, Sweden, Mexico, Denmark, Austria)	**G:** I/C: 97/179 (54%)/ 99/175 (57%) **H:** I/C1/C2: 19/25 (76%)/ 16/25 (64%)/ 19/25 (76%) **I:** I/C: 11/25 (44%)/ 10/23 (43%) **J:** I/C: 21/42 (50%)/ 18/41 (44%) **K:** I/C: 43/76 (57%)/ 42/74 (57%) **L:** I/C: 91/135 (67%)/ 79/133 (59%) **M:** I/C: 7/18 (39%)/ 8/16 (50%) **N:** I/C: 29/49 (59%)/ 25/48 (52%) **O:** I/C: 28/62 (45%)/ 30/60 (50%) **P:** I/C: 11/22 (50%)/ 12/18 (67%) **Q:** I/C: 16/30 (53%)/ 20/32 (63%) **R:** I/C: 27/51 (53%)/ 28/50 (56%) **S:** I/C: 31/47 (66%)/ 31/49 (63%) **T:** not reported	mg/kg i.v. on day 1 and 8 every 3 weeks); I2: gemcitabine (1000 mg/m^2 i.v. on day 1 and 8 every 3 wks for a maximum of 8 cycles) + cisplatin (25 mg/m^2 i.v. on day 1 and 8 every 3 wks for a maximum of 8 cycles) + merestinib (80 mg p.o. q.d.) **X:** gemcitabine (1000 mg/m^2 i.v. on day 1 every 2 wks) + oxaliplatin (100 mg/m^2 i.v. on day 1 every 2 wks)				

	X: 1 hospital in India <u>Source of funding:</u> The review was supported by the Guangxi Natural Science Foundation. The source of funding for the included studies is not reported. <u>Conflicts of interest:</u> The authors of the review declare that there was no conflict of interest for this review.	**U:** I/C: 23/47 (49%)/ 23/49 (47%) **V:** I/C: 33/49 (67%)/ 35/54 (65%) **W:** not reported **X:** I/C: 53/163 (33%)/ 53/163 (33%)					

Evidence table for intervention studies

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison/control (C)	Follow-up	Outcome measures and effect size	Comments
Leone (2016) (Vecti-BIL trial)	Type of study: Multicenter, open-label, randomized phase II trial Setting and country: 12 university hospitals and cancer centers in Italy Source of funding: Amgen provided funding support. This work was supported by grants from the Fondazione Piemontese per l'Oncologia, the Fondazione Piemontese per la Ricerca sul Cancro Onlus, and the Associazione Italiana Ricerca Contro il Cancro. Conflicts of interest: One author has received consulting fees from and has served on advisory	Patients with advanced, non-resectable or metastatic biliary tract cancer and wild-type *KRAS* mutation status Inclusion criteria: • histologically or cytologically documented unresectable or metastatic biliary tract adenocarcinoma either at diagnosis or as a relapse after surgery • wild-type *KRAS* mutation status for the primary or metastatic tumor • ECOG performance status 0-2 • adequate bone marrow, renal and hepatic function Exclusion criteria: • prior systemic treatment,	Gemcitabine (1000 mg/m^2 on day 1 of each 2-wk cycle) + oxaliplatin (100 mg/m^2 on day 2 of each 2-wk cycle) + panitumumab (6 mg/kg on day 1 of each 2-wk cycle)*	Gemcitabine (1000 mg/m^2 on day 1 of each 2-wk cycle) + oxaliplatin (100 mg/m^2 on day 2 of each 2-wk cycle)*	Length of follow-up: Median 10.1 months Loss to follow-up or missing outcome data: All patients were included in the intention-to-treat analysis	*Overall survival* Overall survival for all tumors Months, median I: 9.9 (95%CI: 5.4 to 14.3) C: 10.2 (95%CI: 6.4 to 13.9) HR 0.83 (95%CI: 0.53 to 1.3) Overall survival for intrahepatic cholangiocarcinoma Months, median I: 15.1 (95%CI: 9.3 to 20.9) C: 11.8 (95%CI: 9.2 to 14.4) Overall survival for extrahepatic cholangiocarcinoma and gallbladder carcinoma Months, median I: 7.9 (95%CI: 5.1 to 10.7) C: 8.1 (95%CI: 5.7 to 10.4) *Progression-free survival* Progression-free survival for all tumors (primary endpoint) Months, median I: 5.3 (95%CI: 3.3 to 7.2) C: 4.4 (95%CI: 2.6 to 6.2) HR 0.78 (95%CI: 0.51 to 1.21)	Definitions: * Wild-type *KRAS* mutation status was defined as no mutations in exon 2, codons 12-13. Remarks: - Authors conclusion: The results confirm the marginal role of anti-EGFR therapy even for wild-type *KRAS*-selected biliary tract cancer.

	boards for Celgene, Clovis, Genentech, Lilly, Boehringer-Ingelheim, and Merck Serono outside the submitted work; this author has also received personal fees from Baxalta and grants from Pharma-Mar outside the submitted work. One author has served on advisory boards for Amgen, Bayer, Sanofi-Aventis, Roche, and Ignyta. One author reports personal fees from Amgen and non-financial support from Roche and Eli Lilly outside the submitted work. One author reports personal fees from Amgen outside the submitted work. One author reports non-financial support from Amgen, Merck, and Roche outside the submitted work. One author reports serving as	either chemotherapy or targeted agents • serious comorbidities • unability to fulfill the protocol requirements <u>N total at baseline:</u> Randomized: N = 89 I: N = 45 C: N = 44 <u>Important characteristics:</u> Age, median (range): I: 63.9 y (46.7-78.5) C: 64.2 y (36.8-78.5) Sex, n/N (%) male: I: 17/45 (38%) C: 15/44 (34%) Performance status *0-1* I: 45/45 (100%) C: 43/44 (97.7%) *2* I: 0/45 (0%) C: 1/44 (2.3%)				<u>Progression-free survival for intrahepatic cholangiocarcinoma</u> Months, median I: 5.7 (95%CI: 2.7 to 8.7) C: 6.2 (95%CI: 3.1 to 9.2) <u>Progression-free survival for extrahepatic cholangiocarcinoma and gallbladder carcinoma</u> Months, median I: 4.9 (95%CI: 2.4 to 7.4) C: 3.8 (95%CI: 2.3 to 5.3) *Safety (toxicity grade ≥ 3)* <u>*Anemia*</u> I: 3/45 (6.6%) C: 3/44 (6.8%) <u>*Neutropenia*</u> I: 3/45 (6.6%) C: 2/44 (4.5%) <u>*Thrombocytopenia*</u> I: 1/45 (2.2%) C: 2/42 (4.5%) <u>Skin toxicity</u> I: 6/45 (6.6%) C: 1/44 (2.2%) <u>Conjunctivitis</u> I: 0/45 (0%) C: 0/44 (0%) <u>Ungeal toxicity</u> I: 1/45 (2.2%) C: 0/44 (0%) <u>Neurotoxicity</u>	

	a consultant or on advisory boards for Roche, Sanofi, Marck-Serono, and Eli Lilly outside the submitted work. The other authors declare no competing interests.	Primary tumor site *Intrahepatic bile duct* I: 21/45 (46.7%) C: 21/44 (47.7%) *Extrahepatic bile duct* I: 12/45 (26.7%) C: 7/44 (15.9%) *Gallbladder* I: 12/45 (26.7%) C: 16/44 (36.4%) Groups were comparable at baseline.				I: 2/45 (4.4%) C: 2/44 (4.5%) <u>Diarrhea</u> I: 6/45 (6.6%) C: 3/44 (6.8%) <u>Constipation</u> I: 0/45 (0%) C: 0/44 (0%) <u>Hypokalemia</u> I: 1/45 (2.2%) C: 0/44 (0%)	
Vogel (2018) (PICCA trial)	<u>Type of study:</u> Multicenter, open-label, randomized phase II trial <u>Setting and country:</u> 17 centers in Germany <u>Source of funding:</u> This study was supported by Amgen. <u>Conflicts of interest:</u> One author reports personal fees from Amgen, outside the submitted work.	Patients with advanced biliary tract cancer and wild-type *KRAS* mutation status <u>Inclusion criteria:</u> • age ≥ 18 y • histologically documented cholangiocarcinoma or gallbladder carcinoma • wild-type *KRAS* mutation status • ECOG performance status 0-2 • no prior systemic therapy	Gemcitabine (1000 mg/m^2), cisplatin (25 mg/m^2) and panitumumab (9 mg/kg) on days 1 and 8 of a 21-day cycle	Gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) on days 1 and 8 of a 21-day cycle	<u>Length of follow-up:</u> Not reported. <u>Loss to follow-up or missing outcome data:</u> An intention-to-treat analysis including all 90 randomised patients was included for OS and PFS. 87 (I: 59/C:28) patients received at least one application of study therapy and were included in the toxicity assessment	**Clinical outcomes** <u>Progression-free survival</u> Months, median I: 6.5 C: 8.3 HR 0.73 (95%CI: 0.45-1.21) <u>Overall survival</u> Months, median I: 12.8 C: 20.1 HR 0.70 (95%CI: 0.41-1.18) **Safety** <u>Toxicity grade ≥ 3</u> <u>*Leukopenia*</u> I: 13/59 (22%) C: 8/28 (29%) p = 0.5939 <u>*Neutropenia*</u>	<u>Definitions:</u> * Wild-type *KRAS* mutation status was defined as no mutations in exon 2, codons 12-13. <u>Remarks:</u> - <u>Authors conclusion:</u> Panitumumab in combination with chemotherapy does not improve progression-free survival and overall survival in patients with *KRAS* wild-type, advanced biliary cancer. Genetic profiling should be included in cholangiocarcinoma trials to identify and validate predictive and prognostic biomarkers.

	One author reports personal fees from BMS, MSD, Bayer Health Care and Ipsen, outside the submitted work. One author reports personal fees from Amgen, Merck, Roche, Bayer, Lilly and BMS, outside the submitted work. One author reports personal fees from MSD, BMS, Novartis, Boehringer and Pfizer, grants and personal fees from Roche and AZ, grants from Bruker, outside the submitted work. All other authors do not have any conflict of interest.	• life expectancy ≥ 12 wks <u>Exclusion criteria:</u> Not reported. <u>N total at baseline:</u> Randomized: N = 90 I: N = 62 C: N = 28 <u>Important characteristics:</u> Age, median (range): I: 62 y (18-82) C: 59.5 y (22-76) Sex, n/N (%) male: I: 36/62 (58%) C: 14/28 (50%) Performance status *0* I: 39/62 (63%) C: 17/28 (61%) *1* I: 19/62 (31%) C: 11/28 (39%) *2* I: 2/62 (3%) C: 0/28 (0%) Groups were comparable at baseline, but not				I: 26/59 (44%) C: 13/28 (47%) p = 1.0000 <u>*Febrile neutropenia*</u> I: 3/59 (5%) C: 0/28 (0%) p = 0.5480 <u>*Thrombocytopenia*</u> I: 18/59 (31%) C: 12/28 (43%) p = 0.3350 <u>*Anemia*</u> I: 7/59 (12%) C: 3/28 (11%) p = 1.0000 <u>*Dry skin*</u> I: 3/59 (5%) C: 0/28 (0%) p = 0.5480 <u>*Nail changes*</u> I: 1/59 (2%) C: 0/28 (0%) p = 1.0000 <u>*Rash*</u> I: 7/59 (12%) C: 0/28 (0%) p = 0.0912 <u>*Acne*</u> I: 10/59 (17%) C: 0/28 (0%) p = 0.0268 <u>*Diarrhea*</u> I: 3/59 (5%) C: 0/28 (0%)	

		all patient characteristics could be compared due to unclear reporting.				p = 0.5480 *Mucositis* I: 0/59 (0%) C: 1/28 (4%) p = 0.3218 *Nausea* I: 2/59 (3%) C: 1/28 (4%) p = 1.0000 *Fatique* I: 4/59 (7%) C: 0/28 (0%) p = 0.3005 *Fever* I: 0/59 (0%) C: 0/28 (0%) p = 0.10000 *Infection* I: 6/59 (10%) C: 6/28 (21%) p = 0.1890 *Neuropathy* I: 0/59 (0%) C: 0/28 (0%) p = 0.10000 *Dyspnea* I: 1/59 (2%) C: 0/28 (0%) p = 0.10000	
Oh (2022) TOPAZ-1 trial	Type of study: Multicenter, double-blind randomized phase III trial	Patients with advanced biliary tract cancer Inclusion criteria:	Gemcitabine, cisplatin and durvalumab were administered intravenously on a 21-day	Gemcitabine, cisplatin and placebo were administered intravenously on a 21-day	Length of follow-up: I: Median duration of 16.8 months (95%CI 14.8 to 17.7 months)	Overall survival Months, median I: 12.8 (95%CI 11.1 to 14.0) C: 11.5 (95%CI: 10.1 to 12.5)	Review authors' conclusion The global, phase 3 TOPAZ-1 trial, at a preplanned interim analysis, met the primary objective of a

	Setting and country: 105 centers in 17 countries Source of funding: AstraZeneca sponsored the trial and collaborated with the steering committee on the trial design and collection, analysis, and interpretation of the data. Data analyses were completed by PHASTAR, London, United Kingdom, and AstraZeneca. Durvalumab was provided by AstraZeneca. Conflicts of interest: Several authors reported multiple conflicts of interest	- Adults 18 years of age or older; - histologically confirmed unresectable, locally advanced, or metastatic adenocarcinoma of the biliary tract, - previously untreated disease that was unresectable or metastatic at initial diagnosis as well as those who developed recurrent disease more than 6 months after surgery with curative intent and more than 6 months after the completion of adjuvant therapy; - ECOG performance status of 0 or 1; - one or more measurable lesions per RECIST v1.1;, - no prior exposure to immune-mediated therapy. Exclusion criteria: - ampullary	cycle for up to eight cycles. Durvalumab (1500mg) was administered on day 1 of each cycle, in combination with gemcitabine (1000 mg/m2) and cisplatin (25mg/m^2), which were administered on days 1 and 8 of each cycle.	cycle for up to eight cycles. Placebo (1500mg) was administered on day 1 of each cycle, in combination with gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2), which were administered on days 1 and 8 of each cycle.	C: median duration of 15.9 months (95%CI 14.9 to 16.9) Loss to follow-up or missing outcome data: All patients were evaluated for overall survival and progression-free survival. 338/341 (99%) and 342/342 (99%) received ≥1 dose of study treatment and were included in the safety analysis.	HR 0.80 (95%CI: 0.66 to 0.97; p=0.021) Progression-free survival Months, median I: 7.2 (95%CI: 6.7 to 7.4) C: 5.7 (95%CI: 5.6 to 6.7) HR 0.75 (95%CI: 0.63 to 0.89) *Safety (toxicity grade ≥ 3)* Any grade 3 or 4 event I: 256/338 (75.7%) C: 266/342 (77.8%) Neutropenia I: 65/338 (19.2%) C: 69/342 (20.2%) Anemia I: 64/338 (18.9%) C: 64/342 (18.7%) Thrombocytopenia I: 12/338 (3.6%) C: 18/342 (5.3%) Fatigue I: 9/338 (2.7%) C: 8/342 (2.3%) Leukopenia I: 7/338 (2.1%) C: 2/342 (0.6%) Asthenia I: 4/338 (1.2%) C: 7/342 (2.0%)	statistically significant improvement in overall survival in patients with advanced biliary tract cancer; this occurred with similar percentages of Grade 3 and 4 adverse events in both groups. The trial is ongoing toward completion.

		carcinoma; - active or prior documented autoimmune or inflammatory disorders; - known allergy or hypersensitivity to any study treatment. <u>N total at baseline:</u> Randomized: N = 685 I: N = 341 C: N = 344 <u>Important characteristics:</u> Age, median (range): I: 64 y (20-84) C: 64 y (31-85) Sex, n/N (%) male: I: 169/341 (49.6%) C: 176/344 (51.2%) Primary tumor type Intrahepatic cholangiocarcinoma I: 190/341 (55.7%)					

		C: 193/344 (56.1%) Extrahepatic cholangiocarcinoma I: 66/341 (19.4%) C: 65/344 (18.9%) Gallbladder I: 85/341 (24.9%) C: 86/344 (25.0%) Performance status *0* I: 173/341 (50.7%) C: 163/344 (47.4%) Groups were comparable at baseline					
Kelley (2023) (KEYNOTE-966 study)	<u>Type of study:</u> Multicenter, double-blind randomized phase III trial <u>Setting and country:</u> 175 centres in Asia-Pacific, Europe, North America, and South America <u>Source of funding:</u> The study was funded by Merck	Patients with advanced biliary tract cancer <u>Inclusion criteria:</u> - age 18 years or older; - histologically confirmed unresectable locally advanced or metastatic extrahepatic cholangiocarcinoma (including mixed hepatocellular	Gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 were administered intravenously on days 1 and 8 of 3 week cycles. Pembrolizumab 200 mg was administered intravenously once every 3 weeks	Gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 were administered intravenously on days 1 and 8 of 3 week cycles. Saline placebo was administered intravenously once every 3 weeks	<u>Length of follow-up:</u> Median duration of 25.6 months (95%CI 21.7 to 30.4 months) <u>Loss to follow-up or missing outcome data:</u> All patients were evaluated for overall survival and progression-free survival.	<u>Overall survival</u> Months, median I: 12.7 (95%CI 11.5 to 13.6) C: 10.9 (95%CI: 9.9 to 11.6) HR 0.83 (95%CI: 0.72 to 0.95; p=0.034) Subgroup analyses for overall survival Age <65: HR 0.88 (95% 0.73 to 1.05) ≥65: HR 0.79 (95%CI 0.65 to 0.97) Sex	<u>Review authors' conclusion</u> KEYNOTE966 met its primary endpoint as pembrolizumab plus gemcitabine and cisplatin resulted in a statistically significant, clinically meaningful improvement in overall survival compared with gemcitabine and cisplatin alone without new safety signals in participants with previously untreated metastatic or unresectable biliary tract cancer. Pembro lizumab plus gemcitabine and cisplatin could be a new

	Sharp & Dohme. In collaboration with the academic authors, authors employed by the study funder contributed to study design, data analysis, data interpretation, and writing of the report. The funder maintained the study database and ensured data were collected according to the protocol. <u>Conflicts of interest:</u> An extensive list of potential conflicts of interest is reported	carcinoma and cholangiocarcinoma), gallbladder cancer, or intrahepatic cholangiocarcinoma; - disease measurable per RECIST version1.1; - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; - provided tumour tissue for biomarker assessment; - adequate organ function; - life expectancy of more than 3 months; - the only previous systemic therapy permitted was neoadjuvant or adjuvant therapy completed at least 6 months before the diagnosis of unresectable or metastatic disease.				Female: HR 0.85 (95%CI 0.70 to 1.03) Male: HR 0.83 (95%CI 0.69 to 1.00) Geographical region Asia: HR 0.88 (95%CI 0.72 to 1.08) Not Asia: HR 0.80 (5%CI 0.67 to 0.96) ECOG performance status 0: HR 0.87 (95%CI 0.71 to 1.07) 1: HR 0.84 (95%CI 0.70 to 1.00) Smoking status Current: HR 0.90 (95%CI 0.58 to 1.40) Former: HR 0.87 (95%CI 0.70 to 1.09) Never: HR 0.82 (95%CI 0.68 to 0.98) Antibiotic use within 1 month of study start No: HR 0.86 (95%CI 0.71 to 1.05) Yes: HR 0.81 (95%CI 0.68 to 0.98) Site of origin Extrahepatic: HR 0.99 (95%CI 0.73 to 1.35) Gallbladder: HR 0.96 (95%CI 0.73 to 1.26) Intrahepatic: HR 0.76 (95%CI 0.64 to 0.91) Disease status	treatment option for this population.

		Exclusion criteria: - ampullary cancer; - active autoimmune disease that required systemic treatment in the previous 2 years; N total at baseline: Randomized: N = 1068 I: N = 533 C: N = 536 Important characteristics: Age, median (range): I: 64 y (57-71) C: 63 y (55-70) Sex, n/N (%) male: I: 280/533 (53%) C: 272/536 (51%) Primary tumor type Intrahepatic cholangiocarcinoma I: 320/533 (60%) C: 313/536 (58%) Extrahepatic cholangiocarcinoma I: 98/533 (18%)				Locally advanced: HR 0.69 (95%CI 0.45 to 1.06) Metastatic: HR 0.85 (95%CI 0.74 to 0.98) Biliary stent or drain No: HR 0.85 (95%CI 0.74 to 0.98) Yes: HR 0.72 (95%CI 0.43 to 1.19) Previous chemotherapy No: HR 0.86 (95%CI 0.75 to 0.99) Yes: HR 0.66 (95%CI 0.41 to 1.08) PD-L1 combined positive score <1: HR 0.84 (95%CI 0.62 to 1.14) ≥1: HR 0.85 (95%CI 0.72 to 1.00) Unknown: HR 0.77 (95%CI 0.51 to 1.18) Progression-free survival Months, median I: 6.5 (95%CI: 5.7 to 6.9) C: 5.6 (95%CI: 5.1 to 6.6) HR 0.86 (95%CI: 0.75 to 1.00; p=0.023) *Safety (toxicity grade ≥ 3)* Any grade 3 or 4 event I: 369/529 (70%) C: 367/534 (69%) Decreased neutrophil count Grade 3 I: 167/529 (32%)	

		C: 105/536 (20%) Gallbladder I: 115/533 (22%) C: 118/536 (22%) Performance status *0* I: 258/533 (48%) C: 228/536 (43%) *1* I: 274/533 (51%) C: 308/536 (57%) ≥ *2* I: 1/533 (<1%) C: 0 Groups were comparable at baseline				C: 171/534 (32%) Grade 4 I: 90/529 (17%) C: 82/534 (15%) <u>Anaemia</u> Grade 3 I: 150/529 (28%) C: 150/534 (28%) Grade 4 I: 2/529 (<1%) C: 4/534 (1%) <u>Decreased platelet count</u> Grade 3 I: 64/529 (12%) C: 67/534 (13%) Grade 4 I: 30/529 (6%) C: 40/534 (7%) <u>Fatigue</u> Grade 3 I: 25/529 (5%) C: 22/534 (4%) Grade 4 I: 1/529 (<1%) C: 0 <u>Decreased white blood cell count</u> Grade 3 I: 57/529 (11%) C: 44/534 (8%) Grade 4 I: 4/529 (1%) C: 3/534 (1%)	

Risk of bias assessment

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

Study reference	Appropriate and clearly focused question?[1] Yes No Unclear	Comprehensive and systematic literature search?[2] Yes No Unclear	Description of included and excluded studies?[3] Yes No Unclear	Description of relevant characteristics of included studies?[4] Yes No Unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes No Unclear Not applicable	Assessment of scientific quality of included studies?[5] Yes No Unclear	Enough similarities between studies to make combining them reasonable?[6] Yes No Unclear	Potential risk of publication bias taken into account?[7] Yes No Unclear	Potential conflicts of interest reported?[8] Yes No Unclear
Jiang (2021)	Yes The research question is: 'What is the best treatment strategy for the first-line treatment of patients with advanced biliary tract cancer?'	Unclear The full search strategy is not reported. Instead, MeSH terms are listed. The search was conducted in PubMed, Embase, and Cochrane Library (articles published before August 10, 2020) and resulted in 1668 hits.	No No information is provided about potentially relevant studies that were excluded after reading the full text (n=134)	Yes Relevant characteristics of included studies are provided in Table 1.	Not applicable	Yes Two researchers independently assessed the quality of all included literature based on RCT Cochrane Reviewer bias risk assessment criteria: (1) generation of random sequences; (2) allocation concealment or not; (3) blind method or not; (4) complete results or not; (5) selective reporting or not; (6) other biases. These key points	Unclear	Yes Publication bias was assessed using funnel plots, but the results are not explicitly addressed.	No The review was supported by the Guangxi Natural Science Foundation. The source of funding for the included studies is not reported. The authors of the review declare that there was no conflict of interest for this review.

						are divided into three levels: low risk, high risk, and unclear risk. Differences between investigators are resolved through discussion.			

Based on AMSTAR (Shea BJ, et al. BMC Med Res Methodol. 2007;7:10) and the PRISMA Statement (Moher D, et al. PLoS Med. 2009;6:e1000097).

18. Research question (PICO) and inclusion criteria should be appropriate (in relation to the research question to be answered in the clinical guideline) and predefined.
19. Search period and strategy should be described; at least Medline searched.
20. Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.
21. Characteristics of individual studies relevant to the research question (PICO) should be reported.
22. Quality of individual studies should be assessed using a quality scoring tool or checklist (preferably QUADAS-2; COSMIN checklist for measuring instruments) and taken into account in the evidence synthesis.
23. Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, diagnostic tests (strategy) to allow pooling? For pooled data: at least 5 studies available for pooling; assessment of statistical heterogeneity and, more importantly (see Note), assessment of the reasons for heterogeneity (if present)? Note: sensitivity and specificity depend on the situation in which the test is being used and the thresholds that have been set, and sensitivity and specificity are correlated; therefore, the use of heterogeneity statistics (p-values; I^2) is problematic, and rather than testing whether heterogeneity is present, heterogeneity should be assessed by eye-balling (degree of overlap of confidence intervals in Forest plot), and the reasons for heterogeneity should be examined.
24. There is no clear evidence for publication bias in diagnostic studies, and an ongoing discussion on which statistical method should be used. Tests to identify publication bias are likely to give false-positive results, among available tests, Deeks' test is most valid. Irrespective of the use of statistical methods, you may score "Yes" if the authors discuss the potential risk of publication bias.
25. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes", source of funding or support must be indicated for the systematic review and for each of the included studies.

Risk of bias assessment of intervention studies (randomized controlled trials)

Study reference	**Was the allocation sequence adequately generated?**[a] Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?**[b] Definitely yes Probably yes Probably no Definitely no	**Was knowledge of the allocated interventions adequately prevented?**[c] **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?**[d] Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?**[e] Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?**[f] Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure**[g] LOW SOME CONCERNS HIGH
Leone (2016)	Probably yes; Patients were randomized through a computed system with permuted-block randomization and stratified according to the ECOG performance status and the site of the primary tumor.	Probably yes; Patients were randomized through a computed system. However, it is unclear whether the randomization was performed at a site remote from the trial location.	Definitely no; Open-label study. Participants, investigators, and trial staff were made aware of treatment allocations.	Probably yes; Loss to follow-up was infrequent and reasons for discontinuation of treatment were similar between the groups	Definitely yes; All outcome measures described in the trial register are reported in this article.	Probably yes;	SOME CONCERNS (overall survival, progression-free survival, toxicity)

Vogel (2018)	No information;	No information;	Definitely no; Open-label study	Probably yes; Loss to follow-up was infrequent	Definitely yes; All outcome measures described in the trial register are reported in this article.	Probably yes;	HIGH (overall survival, progression-free survival, toxicity)
Oh (2022)	Probably yes; The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization list will be produced for each of the randomization stratum. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment group.	Definitely yes; Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization. The interactive voice/web response system will provide the kit identification number to be allocated to the patient at the randomization visit and subsequent treatment visits.	Definitely yes; The study will be conducted in a double-blind manner. The patient, the Investigator, and study center staff will be blinded to the durvalumab/placebo allocation and will remain blinded to each patient's assigned study treatment throughout the course of the study. No member of the extended study team at AstraZeneca, at the investigational centers, or any Contract Research Organization handling data will have access to the randomization scheme until the time of the final data analysis (ie, the primary PFS analysis) or any interim analysis data where a decision is made to unblind the study.	Definitely yes; All patients were evaluated for overall survival and progression-free survival. 338/341 (99%) and 342/342 (99%) received ≥1 dose of study treatment and were included in the safety analysis.	Probably no; According to the trial register and the methods section of the paper, quality of life was also assessed but this outcome was not reported.	Probably no; AstraZeneca sponsored the trial and collaborated with the steering committee on the trial design and collection, analysis, and interpretation of the data. Data analyses were completed by PHASTAR, London, United Kingdom, and AstraZeneca. Because a statistically significant improvement in overall survival in the durvalumab arm compared with the placebo arm was observed at the planned interim analysis, the key secondary end point of progression-free survival was formally evaluated at this interim analysis.	SOME CONCERNS (overall survival, progression-free survival, toxicity)
Kelley (2023) (KEYNOTE-966 trial)	Probably yes; Participants were randomly assigned (1:1) to	Definitely yes; Participants were randomly assigned (1:1) to	Definitely yes; Participants, investigators, and those collecting or analysing the	Definitely yes; All patients were evaluated for overall	Definitely yes; All outcome measures described in the trial register are reported in this article.	Probably no; Merck Shard & Dohme funded the study.	SOME CONCERNS (overall survival, progression-free survival, toxicity)

	pembrolizumab or placebo (normal saline) by study investigators using a central interactive voice-response system (Almac Clinical Technologies, Souderton, PA, USA) and a randomisation list generated by the study funder. Randomisation was stratified by geographical region, disease stage, and site of origin.	pembrolizumab or placebo (normal saline) by study investigators using a central interactive voice-response system (Almac Clinical Technologies, Souderton, PA, USA)	data, including representatives of the sponsor, were masked to treatment assignment. Pembrolizumab and saline placebo were packaged identically to ensure participants and investigators remained masked to treatment assignment.	survival and progression-free survival. 529/533 (99%) and 534/536 (99%) received ≥1 dose of study treatment and were included in the safety analysis.		In collaboration with the academic authors, authors employed by the study funder contributed to study design, data analysis, data interpretation, and writing of the report. The funder maintained the study database and ensured data were collected according to the protocol.	

[a] Randomization: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
[b] Allocation concealment: refers to the protection (blinding) of the randomization process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomization (performed at a site remote from trial location). Inadequate procedures are all procedures based on inadequate randomization procedures or open allocation schedules.
[c] Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments, but this should not affect the risk of bias judgement. Blinding of those assessing and collecting outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment or data collection (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is usually not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary. Finally, data analysts should be blinded to patient assignment to prevents that knowledge of patient assignment influences data analysis.
[d] If the percentage of patients lost to follow-up or the percentage of missing outcome data is large, or differs between treatment groups, or the reasons for loss to follow-up or missing outcome data differ between treatment groups, bias is likely unless the proportion of missing outcomes compared with observed event risk is not enough to have an important impact on the intervention effect estimate or appropriate imputation methods have been used.
[e] Results of all predefined outcome measures should be reported; if the protocol is available (in publication or trial registry), then outcomes in the protocol and published report can be compared; if not, outcomes listed in the methods section of an article can be compared with those whose results are reported.
[f] Problems may include: a potential source of bias related to the specific study design used (e.g. lead-time bias or survivor bias); trial stopped early due to some data-dependent process (including formal stopping rules); relevant baseline imbalance between intervention groups; claims of fraudulent behavior; deviations from intention-to-treat (ITT) analysis; (the role of the) funding body. Note: The principles of an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.
[g] Overall judgement of risk of bias per study and per outcome measure, including predicted direction of bias (e.g. favors experimental, or favors comparator). Note: the decision to downgrade the certainty of the evidence for a particular outcome measure is taken based on the body of evidence, i.e. considering potential bias and its impact on the certainty of the evidence in all included studies reporting on the outcome.

Implementatieplan bij module 11 Palliatieve systemische behandeling in de 1e lijn

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Maak samen met de patiënt een afweging om wel of geen palliatieve systeemtherapie te starten. Bespreek de wensen en verwachtingen van de patiënt.	< 1 jaar	Geen is huidige standaard	Bekendheid met richtlijn	Geen is huidige standaard	Publicatie richtlijn	Wetenschappelijke verenigingen	
Geef bij patiënten die in aanmerking komen voor palliatieve systemische therapie gemcitabine + cisplatin.	< 1 jaar	Geen is huidige standaard	Bekendheid met richtlijn	Geen is huidige standaard	Publicatie richtlijn	nvt	
Geef ook gemcitabine + cisplatin bij geconjungeerde hyperbilirubine op basis van galwegobstructie; bij goede drainage is het niet nodig te wachten op normaliseren van het bilirubine.	< 1 jaar	Geen	Bekendheid met richtlijn	Onbekendheid buiten de expertcentra	Publicatie richtlijn	Wetenschappelijke verenigingen	

Overweeg in geval van een contra-indicatie voor cisplatin, substitutie door oxaliplatin of geef gemcitabine monotherapie.	< 1 jaar	Geen is huidige standaard	Bekendheid met richtlijn	Geen is huidige standaard	Publicatie richtlijn	nvt	

Table of excluded studies

Author and year	Reason for exclusion
Reviews	
Kamarajah (2020)	Wrong intervention: neoadjuvant treatment
Belkouz (2019)	Wrong topic: biomarkers for chemotherapy
Lamarca (2019)	Wrong publication type: not a systematic review
Li (2019)	More recent review available
Javle (2019)	Wrong publication type: narrative review
Ying (2019)	Wrong intervention: second-line treatment
Hakeem (2019)	Wrong intervention: neoadjuvant treatment
Zhang (2019)	Wrong publication type: case report and narrative review
Zheng (2019)	More recent review available
Cai (2018)	More comprehensive review available
Zhuang (2017)	More comprehensive review available
Sun (2017)	More comprehensive review available
Zhao (2016)	More comprehensive review available
Vogel (2018)	Wrong publication type: not a systematic review
Chen (2016)	More comprehensive review available
Moriwaki (2016)	Wrong topic: correlation of survival with other outcome measures
Simo (2016)	Wrong intervention: not limited to systemic treatment
Tampellini (2016)	Wrong publication type: not a systematic review
Park (2015)	More comprehensive review available
Boehm (2015)	Wrong intervention: locoregional treatment
Liu (2014)	More comprehensive review available
Valle (2014)	More comprehensive review available
Zhu (2014)	Wrong intervention: adjuvant treatment
Eckel (2014)	More comprehensive review available
Fiteni (2014)	More comprehensive review available
Grendar (2014)	Wrong intervention: neoadjuvant treatment
Lamarca (2014)	Wrong intervention: second-line treatment
Yang (2013)	More comprehensive review available
Sun (2013)	More comprehensive review available
Roth (2012)	Wrong publication type: not a systematic review
RCTs	
Abou-Alfa (2020)	Wrong study design: not an RCT
Abou-Alfa (2020)	Wrong intervention: second-line treatment
Davis (2018)	Wrong study design: not an RCT
Demols (2019)	Wrong publication type: abstract only
Demols (2020)	Wrong intervention: second-line treatment
Javle (2018)	Wrong study design: not an RCT
Kataria (2019)	Wrong publication type: abstract only
Kim (2020)	Wrong intervention: second-line treatment
Kim (2019)	Included in review by Jiang (2021)
Lamarca (2020)	Wrong study design: not an RCT (post-hoc analysis)
Morizane (2019)	Included in review by Jiang (2021)
Yoon (2018)	Wrong publication type: abstract only
Zheng (2018)	Wrong intervention: second-line treatment
Chiang (2018)	Wrong study design: not an RCT
Feng (2020)	Wrong study design: not an RCT
Harding (2019)	Wrong publication type: abstract only

Hollebecque (2018)	Wrong study design: not an RCT
Ikeda (2018)	Wrong study design: not an RCT
Iyer (2018)	Wrong study design: not an RCT
Javle (2018)	Wrong publication type: abstract only
Jensen (2020)	Wrong study design: not an RCT
Kim (2019)	Wrong study design: not an RCT
Kim (2018)	Wrong study design: not an RCT
Kim (2020)	Wrong study design: not an RCT
Kim (2020)	Wrong study design: not an RCT
Klein (2020)	Wrong study design: not an RCT
Larsen (2018)	Wrong study design: not an RCT
Markussen (2020)	Included in review by Jiang (2021)
Okano (2020)	Wrong study design: not an RCT
Perkhofer (2019)	Wrong publication type: study protocol
Sahai (2018)	Wrong study design: not an RCT
Sgouros (2020)	Wrong study design: not an RCT
Shroff (2019)	Wrong study design: not an RCT
Subbiah (2020)	Wrong study design: not an RCT
Sun (2019)	Wrong study design: not an RCT
Yoo (2018)	Wrong study design: not an RCT
Javle (2019)	Wrong publication type: study protocol
Yang (2020)	Wrong intervention: systemic treatment and locoregional treatment

Literature search strategy for systematic reviews

Embase (via Embase.com)
'biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR 'bile duct') NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ab,ti,kw AND [english]/lim AND [2012-2019]/py NOT 'conference abstract':it NOT ([animals]/lim NOT [humans]/lim) AND ('systematic review'/exp OR 'meta analysis'/exp OR (((systematic*) NEAR/3 (review)) OR meta-analy* OR metaanaly*):ab,ti,kw)

481 hits

Medline (via OVID)
exp Gallbladder Neoplasms/ or exp biliary tract neoplasms/ or exp bile duct neoplasms/ or exp cholangiocarcinoma/ or exp klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile duct) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ab,ti,kf.
AND english.la.
AND (2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020)
NOT (exp animals/ NOT humans/)
AND (Systematic Review/ OR Meta-Analysis/ OR (((systematic*) ADJ3 (review)) OR meta-analy* OR metaanaly*).ab,ti,kf.)

251 hits

Literature search strategy for RCTs
Embase (via Embase.com)
('biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin*):ti,kw) AND [english]/lim AND [2015-2020]/py NOT 'conference abstract':it NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) AND (('clinical trial'/exp OR (trial):ab,ti,kw) OR [clinical trial number]/lim)

766 hits

Medline (via OVID)
(exp *Gallbladder Neoplasms/ or exp *biliary tract neoplasms/ or exp *bile duct neoplasms/ or exp *cholangiocarcinoma/ or exp *klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ti,kf.) AND english.la. AND 2015:2020.(sa_year). NOT (exp animals/ NOT humans/) AND ((Clinical Trial/ OR (trial).ab,ti,kf.) OR clinicaltrials.si.)

422 hits

Cochrane Central Register of Controlled Trials (via Wiley)
((((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ti)

643 hits

Module 12 Palliatieve systemische behandeling na de 1e lijn

Uitgangsvraag
Wat is de rol van palliatieve systemische behandeling als tweede- of derdelijnsbehandeling bij (verschillende subgroepen van) patiënten met een lokaal gevorderd of gemetastaseerd galweg- of galblaascarcinoom?

Inleiding
In de vorige richtlijn (2013) werden geen tweedelijns behandelingen opgenomen bij gebrek aan bewijs. Sinds 2013 zijn er meerdere studies afgerond in de tweede lijn. Omdat een aantal tweedelijns behandelingen in een geselecteerde populatie verricht werd op basis van moleculair onderzoek, wordt ook de plaatsbepaling van moleculair onderzoek beschreven.

Search and select
A systematic review of the literature was performed to answer the following question:
What are the (un)beneficial effects of second- and third-line palliative systemic therapy in (specific subgroups of) patients with a locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma?

P: patients with locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma
I: second- or third-line palliative systemic therapy
C: best supportive care
O: overall survival, quality of life, progression-free survival, toxicity

Relevant outcome measures
The working group considered overall survival and quality of life as critical outcome measures for decision making; and progression-free survival and toxicity as important outcome measures for decision making.

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

The working group defined the following minimal clinically (patient) relevant differences (using the PASKWIL criteria for palliative treatment with OS standard arm ≤ 12 months where possible and other criteria):

- Overall survival: absolute difference in OS > 12 weeks and hazard ratio (HR) < 0.7.
- Quality of life: absolute difference ≥ 10 points on the EORTC QLQ-C30 or a difference of a similar magnitude on other disease-specific quality of life questionnaires.
- Toxicity: ≥ 5% difference in fatal adverse events, ≥ 25% difference in grade ≥ 3 adverse events.

Search and select (Methods)
For the current update of this guideline, two broad systematic literature searches were performed for publications involving patients with biliary tract cancer. First, the databases Medline (via OVID) and Embase (via Embase.com) were searched using relevant search terms for systematic reviews published between January 1st 2012 and December 31st 2019 for Medline and between January 1st 2012 and August 31rd 2020 for Embase. Second, the databases Medline (via OVID), Embase (via Embase.com) and Cochrane Central Register of Controlled Trials (via Wiley) were searched for RCTs published between January 1st 2015 and October 12th 2020. The detailed search strategies are depicted under the tab Methods.

The systematic literature searches resulted in 547 unique hits for systematic reviews. A preselection of systematic reviews was made by advisors affiliated with the Knowledge Institute of the Dutch Association of Medical Specialists, based on study population and study design. An inclusive approach was taken, meaning that in case of doubt about the eligibility of a particular publication, this publication was included in the preselection. In total, 74 systematic reviews related to palliative systemic treatment were included in the preselection. Subsequently, publications were screened based on title and abstract using the following selection criteria: (a) full text publication in English or Dutch; (b) systematic review of RCTs; (c) involving patients with a non-resectable, locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma; and (d) comparing at least one of the aforementioned outcome measures between patients who received palliative systemic therapy and patients who received best supportive care. This resulted in 31 systematic reviews. After reading the full text, all of these reviews were excluded (see the table with reasons for exclusion under the tab Methods).

The review by Ying (2019) performed a systematic search in April 2018 for studies about second-line treatment for advanced biliary tract cancer. This study did not identify relevant RCTs and was therefore excluded. The guideline working group decided to update this search to identify recent RCTs. Advisors affiliated with the Knowledge Institute of the Dutch Association of Medical Specialists made a preselection of RCTs from the two broad systematic literature searches published between 2018 and 2021. Following a similar inclusive approach as described above, 49 publications were included in the preselection. These publications were screened based on title and abstract using the following selection criteria: (a) full text publication in English or Dutch; (b) RCT; (c) involving patients with a locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma; and (d) comparing at least one of the aforementioned outcome measures between patients who received palliative systemic therapy and patients who received best supportive care. This resulted in 39 publications. After reading the full text, 37 studies were excluded (see the table with reasons for exclusions under the tab Methods), and two studies were included (Abou-Alfa, 2020; Demols, 2020). In addition, members of the working group put forward two additional publications on the effects of second- or third-line palliative systemic treatment that were published after the end date used in the broad systematic literature search (Lamarca, 2021; Zhu, 2021). The paper by Zhu (2021) presented the final overall survival results for the ClarIDHy trial, which was also reported by Abou-Alfa (2020).

Results

Four publications reporting the results of three RCTs were included in the analysis of the literature (Abou-Alfa, 2020; Demols, 2020; Lamarca, 2021; and Zhu, 2021). Three types of systemic treatment were evaluated: ivosidenib (Abou-Alfa, 2020; Zhu, 2021), regorafenib (Demols, 2020), and FOLFOX chemotherapy (folinic acid, fluorouracil, and oxaliplatin) (Lamarca, 2021). Important study characteristics and results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature

Description of studies

Abou-Alfa (2020) conducted a randomized double-blind placebo-controlled phase III trial (the ClarIDHy study) in 49 hospitals in six countries. This study aimed to assess the efficacy and safety of ivosidenib in patients with IDH1-mutant cholangiocarcinoma who had previously received up to two lines of treatment with one gemcitabine-based or fluorouracil-based chemotherapy. Patients were randomized (2:1) to receive either oral ivosidenib (500

mg) (n=124) or placebo once daily in 28-day cycles (n=61). In the placebo group, 43 patients crossed over to ivosidenib upon disease progression. Outcome measures included overall survival, quality of life, progression-free survival, and toxicity.
Zhu (2021) reported the final results for the ClarIDHy study. Outcome measures included overall survival, quality of life, and toxicity.

Demols 2020 conducted a randomized double-blind placebo-controlled phase II trial (the REACHIN trial) in 12 centers in Belgium. This study aimed to evaluate the efficacy and safety of regorafenib in patients with locally advanced or metastatic biliary tumors who experienced disease progression after gemcitabine and platinum-based chemotherapy delivered in one of multiple lines. Patients were randomized (1:1) to receive best supportive care and either oral regorafenib (160 mg during three weeks of a 4-week cycle) (n=33) or placebo (n=33). Tumor samples were collected for FRFR2 fusion testing, 43 patients had available samples and there was one patient with a FGFR2 fusion in the regorafenib arm. Outcome measures included overall survival, progression-free survival, and toxicity.

Lamarca (2021) conducted a randomized open-label phase III trial (the ABC-06 trial) in 20 centres in the United Kingdom. This study aimed to evaluate the efficacy of adding second-line chemotherapy with FOLFOX to active symptom control for patients with advanced biliary tract cancer who experienced disease progression after first-line treatment with gemcitabine and cisplatin. Patients were randomized (1:1) to receive either FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and active symptom control (n=81) or active symptom control alone (n=81). Outcome measures included overall survival, progression-free survival, and toxicity.

Results

Overall survival

Overall survival was reported in all three trials.

Abou-Alfa (2020) reported that after a median of 6.9 months follow-up (January 2019), the median overall survival was 10.8 months (95%CI 7.7 to 17.6) in the group that received ivosidenib and 9.7 months (95%CI 4.8 to 12.1) in the group that received placebo (of whom 35 out of 61 received ivosidenib on radiological progression). The hazard ratio was 0.69 (95%CI 0.44 to 1.10). Using the rank-preserving structural failure time method to reconstruct the survival curve for patients in the placebo group to correct for crossover to ivosidenib, the adjusted median overall survival was 6.0 months (95%CI 3.6 to 6.3) in the placebo group (HR 0.46; 95%CI 0.28 to 0.75; p=0.0008).
With a data cut-off in May 2020, **Zhu (2021)** reported that the median overall survival was 10.3 months (95%CI 7.8 to 12.4) in the group that received ivosidenib and 7.5 months (95%CI 4.8 to 11.1) in the placebo group. The hazard ratio was 0.79 (95%CI 0.56 to 1.12). When adjusted for the effect of 43 patients crossing over from the placebo group to the ivosidenib group, median overall survival was 5.1 months (95%CI 3.8 to 7.6) in the placebo group. The hazard ratio was 0.49 (95%CI 0.34 to 0.70; p<0.001).
The difference in survival data as reported by Zhu (2021) was considered not clinically relevant as the gain in overall survival was just over 12 weeks but the hazard ratio was > 0.7: 0.79 (95%CI 0.56 to 1.12).

Demols (2020) reported that median overall survival was 5.3 months (95%CI 2.7 to 10.5) in the group that received regorafenib and 5.1 months (95%CI 3.0 to 6.4) in the placebo group. This difference was considered not clinically relevant, as the gain in median overall survival was less than 12 weeks and the hazard ratio was > 0.7: 0.77 (95%CI 0.45 to 1.31).

Lamarca (2021) reported that median overall survival was 6.2 months (95%CI 5.4 to 7.6) in the group that received FOLFOX and active symptom control and 5.3 months (95%CI 4.1 to 5.8) in the group that received active symptom control alone. This difference was considered not clinically relevant, as the gain in median overall survival was less than 12 weeks, although the hazard ratio (adjusted for platinum sensitivity, serum albumin concentration, and disease stage) was < 0.7: 0.69 (95%CI 0.50 to 0.97; p=0.031.

Quality of life

Quality of life was reported by **Abou-Alfa (2020)** and **Zhu (2021)** for the ClarIDHy trial. No clinically relevant differences (≥ 10 points) were found for global health status assessed using the EORTC QLQ-C30. Clinically relevant differences were found for two out of five functional subscales: physical and emotional functioning (differences in favour of ivosidenib from baseline to cycle 2 and cycle 3). In addition, clinically relevant differences were found for two out of nine symptoms subscales: pain and dyspnea (difference in favour of ivosidenib from baseline to cycle 2). Zhu (2021) also reported quality of life assessed using the EORTC QLQ-BIL21. Clinically relevant differences were reported for two out of eight subscales: anxiety and tiredness (differences in favour of ivosidenib from baseline to cycle 2).

Progression-free survival

Progression-free survival was reported in all three trials.

Abou-Alfa (2020) reported that median progression-free survival was 2.7 months (95%CI 1.6 to 4.2) in the group that received ivosidenib and 1.4 months (95%CI 1.4 to 1.6) in the group that received placebo. The hazard ratio was 0.37 (95%CI 0.25 to 0.54; p<0.0001). Overall survival was less than 12 months in the control group, therefore the clinical relevance of progression-free survival was not considered, according to the PASKWIL criteria (2023).

Demols (2020) reported that median progression-free survival was 3.0 months (95%CI 2.3 to 4.9) in the group that received regorafenib and 1.5 months (95%CI 1.2 to 2.0) in the group that received best supportive care alone. The hazard ratio was 0.49 (95%CI 0.29 to 0.81); p=0.004). Overall survival was less than 12 months in the control group, therefore the clinical relevance of progression-free survival was not considered, according to the PASKWIL criteria (2023).

Lamarca (2021) reported that median progression-free survival was 4.0 months (95%CI 3.2 to 5.0) in the group that received FOLFOX and active symptom control. Progression-free survival for the group that received only active symptom control was not reported. Overall survival was less than 12 months in the control group, therefore the clinical relevance of progression-free survival was not considered, according to the PASKWIL criteria (2023).

Toxicity

Toxicity was reported in all three trials.

Zhu (2021) reported that 62 out of 123 patients (50%) in the group that received ivosidenib and 22 out of 59 patients (37%) in the group that received placebo (before crossover) experienced any grade ≥ 3 treatment-emergent adverse event. Grade ≥ 3 events that occurred in more than 5% of patients included ascites (11/123 [9%] in the ivosidenib group versus 4/59 [7%] in the placebo group), anemia (8/123 [7%] versus 0/59 [0%]), increased bilirubin level (7/123 [6%] versus 1/59 [2%]), hyponatremia (7/123 [6%] versus 6/59 [10%]), hypophosphatemia (4/123 [3%] versus 3/59 [5%]), and increased ALP level (3/123 [2%] versus 3/59 [5%]). None of the differences fulfill the minimal clinically (patient) relevant difference of >25% between the groups.

Demols (2020) reported that 12 out of 33 patients in the group that received regorafenib (36%) and 8 out of 33 patients in the placebo group (24%) experienced any grade ≥ 3 adverse event. This difference does not fulfill the minimal clinically (patient) relevant difference of > 25% between the groups.

Lamarca (2021) reported that 56 out of 81 patients in the group that received FOLFOX (69%) and active symptom control and 42 out of 81 patients in the group that received only active symptom control (52%) experienced any grade ≥ 3 adverse event. Grade ≥ 3 events that occurred in more than 5% of patients included neutropenia (10/81 [12%] in the FOLFOX and active symptom control group versus 1/81 [1%] in the active symptom control group), fatigue/lethargy (15/81 [19%] versus 6/81 [7%]), infection (14/81 [17%} versus 3/81 [4%]), biliary events (15/81 [18%] versus 15/81 [18%]), hypertension (4/81 [5%] versus 1/81 [1%]), vomiting (3/81 [4%] versus 4/81 [5%]), anorexia (1/81 [1%] versus 6/81 [7%]), pain (8/81 [10%] versus 6/81 [7%]), and thromboembolic event (0/81 [0%] versus 4/81 [5%]). None of the differences fulfill the minimal clinically (patient) relevant difference of >25% between the groups.

Level of evidence of the literature

The evidence was derived from five publications reporting the results of four RCTs. Therefore, the level of evidence for all reported outcome measures started at 'high quality'.

Overall survival: ivosidenib (Abou-Alfa, 2020; Zhu, 2021)

The level of evidence regarding the outcome measure overall survival was downgraded by three levels because of study limitations (-1; risk of bias because of potential conflicts of interest), applicability (-1; indirectness because most patients in the placebo group crossed over to ivosidenib upon disease progression) and number of included patients (-1; imprecision because the 95% confidence interval of the hazard ratios cross the boundary of clinical relevance).

Overall survival: regorafenib (Demols, 2020)

The level of evidence regarding the outcome measure overall survival was downgraded by three levels because of the number of included patients (-3; imprecision because the hazard ratio includes the possibility of a clinically relevant difference, hazards did not appear proportional over time and the analysis was based on only 30 deaths in each group).

Overall survival: FOLFOX (Lamarca, 2021)

The level of evidence regarding the outcome measure overall survival was downgraded by one level because of the number of included patients (-1; imprecision because the hazard ratios [also for the subgroups] cross the boundary of clinical relevance).

Quality of life
The level of evidence regarding the outcome measure quality of life was downgraded by three levels because of study limitations (-2 risk of bias because of considerable loss to follow-up); number of included patients (-1 imprecision because the 95% confidence intervals cross the boundary of clinical relevance).

Toxicity
The level of evidence regarding the outcome measure toxicity was downgraded by two levels because of the number of included patients (-2 imprecision because of the low numbers of patients [experiencing a grade ≥ 3 adverse event]).

Conclusions

Ivosidenib: overall survival (critical outcome measure)

Very low GRADE	The evidence is very uncertain about the effect of ivosidenib as second- or third-line palliative systemic therapy on **overall survival** when compared with placebo in patients with *IDH1*-mutant cholangiocarcinoma. *Source: Abou-Alfa, 2020; Zhu, 2021;*

Ivosidenib: quality of life (critical outcome measure)

Very low GRADE	The evidence is very uncertain about the effect of ivosidenib as second- or third-line palliative systemic therapy on **quality of life** when compared with placebo in patients with *IDH1*-mutant cholangiocarcinoma. *Source: Abou-Alfa, 2020; Zhu, 2021;*

Ivosidenib: toxicity (important outcome measure)

Low GRADE	Second- or third-line palliative systemic therapy with ivosidenib may result in little to no difference in grade ≥ 3 **toxicity** when compared with placebo in patients with *IDH1*-mutant cholangiocarcinoma. *Source: Abou-Alfa, 2020; Zhu, 2021;*

Regorafenib: overall survival (critical outcome measure)

Very low GRADE	The evidence is very uncertain about the effect of regorafenib on **overall survival** when compared with placebo in patients with locally advanced or metastatic biliary tumors who experienced disease progression after gemcitabine and platinum-based chemotherapy. *Source: Demols, 2020;*

Regorafenib: quality of life (critical outcome measure)

No GRADE	No evidence is available about the effect of regorafenib as second- or third-line palliative systemic therapy on **quality of life** when compared with placebo in patients with locally advanced or metastasized cholangiocarcinoma or gallbladder carcinoma.

Regorafenib: toxicity (important outcome measure)

Low GRADE	Second- or third-line palliative systemic therapy with regorafenib may result in little to no difference in grade ≥ 3 **toxicity** when compared with placebo in patients with locally advanced or metastatic biliary tumors who experienced disease progression after gemcitabine and platinum-based chemotherapy. *Source: Demols, 2020;*

FOLFOX: overall survival (critical outcome measure)

Moderate GRADE	FOLFOX as second-line palliative systemic therapy likely results in little to no difference in **overall survival** when compared with active symptom control in patients with advanced biliary tract cancer who experienced disease progression after first-line treatment with gemcitabine and cisplatin. *Source: Lamarca, 2021;*

FOLFOX: quality of life (critical outcome measure)

No GRADE	No evidence is available about the effect of FOLFOX as second- or third-line palliative systemic therapy on **quality of life** when compared with best supportive care in patients with advanced biliary tract cancer who experienced disease progression after first-line treatment with gemcitabine and cisplatin.

FOLFOX: toxicity (important outcome measure)

Low GRADE	Second- or third-line palliative systemic therapy with FOLFOX may result in little to no difference in grade ≥ 3 **toxicity** when compared with active symptom control in (subgroups of) patients with advanced biliary tract cancer who experienced disease progression after first-line treatment with gemcitabine and cisplatin *Source: Lamarca, 2021*

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

FOLFOX was de enige tweedelijns behandeling die voldeed aan de PASKWIL criteria voor voldoende effectiviteit uit 2016 in patiënten met een lokaal gevorderd of gemetastaseerd galwegcarcinoom (Lamarca, 2021). De hazard ratio voldeed net aan de criteria (HR 0.69 [95%CI 0,50 tot 0,97; p=0.031]), echter de absolute winst in mediane overleving met FOLFOX was slechts 0,9 maanden (6,2 maanden (95%BI 5,4 tot 7,6) FOLFOX versus 5,3 maanden (95%BI 4,1 tot 5,8) met actieve symptoombestrijding. De behandeling voldoet niet aan de in deze module voorafgedefineerde criteria voor effectiviteit. De bewijskracht was redelijk. Opgemerkt dient te worden dat de controlegroep een onverwachts lange overleving toonde en daarmee een mogelijke verklaring is voor de beperkte absolute winst van FOLFOX. Bij het ontwerp van de studie werd uitgegaan van de overleving in de controlegroep van 4 maanden. De resultaten van de controlegroep kunnen ook als pleidooi gebruikt worden om de gestandaardiseerde 'best supportive care' volgens de studie toe te passen. Deze bestond uit vierwekelijkse controles met controle van leverwaarden en eventuele interventies op het gebied van enzymsuppletie, maaguitgangstenose, galwegobstructie en cholangiosepsis.

Op dit moment is er geen doelgerichte therapie specifiek voor het galweg-en galblaascarcinoom als standaardzorg in Nederland beschikbaar. Net zoals bij talrijke andere tumortypen, is er ook bij het galweg- en galblaascarcinoom een ontwikkeling gaande waarbij systeemtherapie gericht wordt op moleculaire markers in plaats van anatomische locatie alleen. Dit heeft als consequentie dat er vele kleine subpopulaties ontstaan. Studies die verricht worden om effectiviteit aan te tonen in deze subgroepen, zijn daarom vaak kleinere eenarmige studies. Daarop is ingespeeld door aangepaste PASKWIL criteria te ontwerpen voor eenarmige fase 2 studies met als doel om ook deze studies te beoordelen voor vergoeding op de Nederlandse markt. Opvallend is dat de anatomische locaties verschillen vertonen in het voorkomen van deze moleculaire markers. Met name bij het intrahepatische cholangiocarcinoom (iCCA) zijn er veel targets beschikbaar waarmee onderzoek verricht is en wordt.

Bij patiënten met een iCCA komt bij 15% een IDH-1 mutatie voor. Ivosidenib werd onderzocht als tweede- or derdelijnsbehandeling voor patiënten met een *IDH1*-gemuteerd cholangiocarcinoom in vergelijking met placebo (Abou-Alfa, 2020; Zhu, 2021). Het primaire eindpunt van de studie is PFS en voldoet daarmee niet aan de criteria van voldoende werkzaamheid, echter de plaatsbepaling is nog niet duidelijk omdat de studie nog niet officieel beoordeeld is. Patiënten met een *IDH1*-mutatie worden bij voorkeur in studieverband behandeld. Naast de progressievrije overleving werd ook overleving gerapporteerd. In de intention to treat analyse was de mediane overleving 10,8 maanden (95% BI 7,7 tot 17,6) met ivosidenib versus 9,7 maanden (95%BI 4,8 tot 12,1) in de placebogroep. Er is gecorrigeerd voor het cross-over design van de studie. Er werd geen klinisch relevant verschil gevonden voor 'global health' gemeten met behulp van de EORTC QLQ-C30 vragenlijst, voor twee van de vijf functionele schalen (fysiek en emotioneel functioneren) werden klinisch relevante verschillen ten gunste van behandeling met ivosidenib gevonden.

Andere behandelingen in tweede lijn
Er zijn twee zeer effectieve behandelingen beschikbaar op basis van twee verschillende predictieve makers die niet specifiek zijn voor het galweg- en galblaascarcinoom, maar binnen alle tumorsoorten voorkomen. De eerste marker is mismatch repair deficiëntie (dMMR) of MSI-H (microsatellite instability high), wat bij <1% bij patiënten met galweg- en of galblaascarcinoom voorkomt. In de fase 2 Keynote-158 studie waarin patiënten met

dMMR of MSI-H in tweede lijn of later behandeld werden met pembrolizumab (Marabelle, 2020) werd een response rate voor alle patiënten gerapporteerd van 34,3% (95% CI 28,3-tot 40.8%). De mediane progressievrije overleving was 4,1 maanden (95% BI: 2,4 tot 4,9) en de mediane overleving was 23,5 maanden (95% BI, 13.5 tot [nog niet bereikt], follow up 13,4 maanden). Ongeveer 10% van de geïncludeerde patiënten had een galweg- of galblaascarcinoom. Daarnaast werden in de enkelarmige, niet gepubliceerde DRUP studie patiënten met lokaal gevorderde en gemetastaseerde solide dMMR/MSI tumoren behandeld met nivolumab (Zorginstituut Nederland, 2022). Bij een mediane follow-up duur van 11,5 maanden (95% BI 10,2 – 13,6) was de mediane OS nog niet bereikt. De mediane PFS bedroeg 18 maanden (95% BI 7 – niet bereikt). 50 van de 137 patiënten hadden een respons (ORR 36,5% [95% BI 28,4 – 45,1]). Schattingen van de mediane duur van de respons variëren tussen de 62-69 maanden. Van de geïncludeerde patiënten had 3% een galwegcarcinoom. Het Zorginstituut concludeert op basis van de data dat “nivolumab een meerwaarde heeft ten opzichte van best ondersteunende zorg bij volwassen patiënten met lokaalgevorderde of gemetastaseerde solide dMMR/MSI tumoren die hebben gefaald op de standaardbehandeling(en) of waarbij geen standaardbehandeling bestaat of geïndiceerd is. Nivolumab voldoet daarmee aan de stand van de wetenschap en praktijk”.

De tweede predictieve marker is NTRK (neurotrophic proteine receptor kinase) fusie wat bij minder dan 0.1 % van de patiënten met een galweg- of galblaascarcinoom voorkomt (Drilon, 2018). Ook dit was een eenarmige fase 1-2 studie waarin patiënten met een NTRK-fusie met larotrectinib behandeld werden. De ORR was 75% (95% CI: 61 tot 85); 13% van de patiënten had een complete respons, 62% een partiële respons en slechts 9% progressieve ziekte. Slechts 2% (4 patiënten) had een cholangiocarcinoom.

Er zijn al talrijke studies die zich richten op FGFR-fusie gen bij het iCCA. Een van deze studies is de recent gepubliceerde een-armige fase studie waarin patiënten die progressief waren op minstens één lijn systeemtherapie behandeld werden met futibatinib (Goyal, 2023). De ORR was 42%; 95% BI 32% tot 52%), en de mediane duur van respons was 9,7 maanden. Futibatinib is nog niet beoordeeld in NL.

Aanvullend onderzoek

Vanwege het ontbreken van een reguliere behandeling/vergoeding op basis van markers, zijn er binnen de standaardzorg, behalve de aanwezigheid van NTRK-fusie en dMMR geen andere aanvullende bepalingen te adviseren. Echter voor een selectie van patiënten (met name patiënten met iCCA) die in goede conditie zijn en gemotiveerd zijn voor een behandeling in studieverband kan het inzetten van brede moleculaire testen waarmee ook NTRK-fusie en dMMR opgespoord kan worden, wel worden overwogen. Dit is vanwege het feit dat deze twee relatief weinig voorkomen, maar er door het breder inzetten van moleculaire testen er wel een reële kans is op het detecteren van een andere targetable genafwijking (De Bitter, 2022; Valle, 2017; Zimmer, 2023) die in studieverband behandeld kan worden (zoals de DRUP-studie). Deze testen betreffen een targeted RNA sequencing test (zoals Archer) en een breed targeted mutatie panel via NGS (zoals TSO-500 of whole exome sequencing). Experts ontwikkelen een lijst van Klinisch Noodzakelijke Targets (KNT).

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Tijdens het ziektebeloop dienen er steeds keuzes gemaakt te worden over de toe te passen behandelingen. Dit dient plaats te vinden op basis van Samen Beslissen. Tijdens gedeelde besluitvorming worden de voor -en nadelen benoemd en tegen elkaar afgewogen. Er wordt

afgetast of er vragen zijn over effectiviteit van de behandeling. Daarnaast dient er informatie gegeven te worden over de bijwerkingen en de invloed op de kwaliteit van leven. Gedeelde besluitvorming geeft bij de patiënt en zijn naasten een grotere mate van tevredenheid, gelet op de ervaren betrokkenheid bij de besluitvorming en de daarbij ervaren emotionele ondersteuning.

Kosten (middelenbeslag)
De combinatie van gemcitabine met cisplatin is kosteneffectiever dan gemcitabine alleen (Roth, 2012). Deze analyse is niet voor tweedelijns FOLFOX verricht. Maar op deze chemotherapeutica rust geen patent meer en hebben daarmee een verwaarloosbare invloed op het ziekenhuiskostenbudget. Slechts een kwart van de mensen die niet in aanmerking komen voor resectie start met eerstelijns palliatieve systeemtherapie (NKR 2017-2021). Slechts weer een zeer klein aandeel is nog in voldoende conditie voor een tweedelijns behandeling. Rekening houdend dat bijvoorbeeld slechts 10-15% een FGFR-fusie heeft, komt dit neer op minder dan 10 patiënten per jaar, daarmee is de verwachting dat de invloed verwaarloosbaar zal zijn op het ziekenhuisbudget. Van belang is alleen die patiënten te behandelen die voldeden aan de inclusie- en exclusiecriteria van de studie om de winst uit de studies ook in de dagelijkse praktijk terug te zien.

Aanvaardbaarheid, haalbaarheid en implementatie
Omdat de opties in tweede lijn beperkt zijn en de ontwikkelingen van diagnostiek en behandeling telkens veranderen, is het belangrijk dat iedereen in Nederland over dezelfde mogelijkheden voor behandeling in studiebehandeling geïnformeerd wordt.
Daarvoor is het belangrijk dat elk ziekenhuis patiënten bespreekt in een multidisciplinair regionaal MDO met aanwezigheid van een academische partner. Vooralsnog is de uitgebreide diagnostiek middels NGS geen vergoede zorg in Nederland. De aanbevelingen zijn in overeenstemming met de huidige zorg.

Aanbevelingen
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Vooralsnog is er geen goede onderbouwing of de doelgerichte therapie in studieverband de voorkeur heeft boven FOLFOX omdat er geen direct vergelijkende studies verricht zijn. Alhoewel behandeling met FOLFOX in tweedelijn de enige studie met enige bewijslast is, heeft de werkgroep de voorkeur bij vitale en gemotiveerde patiënten aanvullende onderzoek naar predictieve markers te verrichten voor participatie in klinisch onderzoek. Hiervoor dienen patiënten verwezen worden naar een academisch centrum vanwege de toegang tot studiebehandelingen voor deze zeldzame kanker. Dit heeft te maken met de snelle ontwikkelingen van zinvolle biomarkers op dit gebied, maar ook de lastige toegang tot deze middelen. Tijdens deze analyse kan behandeling met FOLFOX versus actieve symptoom bestrijding overwogen worden.

Bepaal met behulp van Samen Beslissen of tweedelijns behandeling gestart dient te worden.

Bespreek de mogelijkheid van actieve symptoombestrijding indien er besloten wordt geen tumorgerichte tweedelijns behandeling te starten. Actieve symptoombestrijding zoals in de ABC-06 studie bestond uit elke 4 weken fysieke controle met leverwaarden en onder andere eventuele behandeling enzymsuppletie, maaguitgangstenose, galwegobstructie en cholangiosepsis.

Bespreek bij wens voor tweedelijns palliatieve systeemtherapie de behandeling met FOLFOX en bespreek ook dat deze winst gemiddeld beperkt is.

Overleg indien tweedelijns behandeling wordt overwogen met een centrum met voldoende expertise welke studies voorhanden zijn en welke aanvullende bepalingen (o.a. MSI, NTRK) verricht dienen te worden.

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Bijlagen bij module 12 Palliatieve systemische behandeling na de 1e lijn

Evidence tables

Evidence table for intervention studies

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison/control (C)	Follow-up	Outcome measures and effect size	Comments
Abou-Alfa (2020) Zhu (2021) (ClarIDHy trial)	Type of study: Multicenter, randomized, double-blind, placebo-controlled, phase III trial Setting and country: 49 hospitals in 6 countries (France, Italy, South Korea, Spain, UK, and USA) Source of funding: This study was supported by Agios Pharmaceuticals. The funder had a role in study design, data collection, data analysis, and data interpretation, but this is not further specified. Medical writing support	Patients with advanced cholangiocarcinoma and an *IDH1* mutation Inclusion criteria: • age ≥ 18 y • histologically confirmed, advanced, cholangiocarcinoma • *IDH1* mutation • up to 2 previous treatment regimens for advanced disease (unresectable or metastatic), with 1 gemcitabine-based or fluorouracil-based chemotherapy and no previous mutant IDH inhibitor therapy	Ivosidenib (500 mg orally once daily in continuous 28-day cycles)	Placebo (orally once daily in continuous 28-day cycles)	Length of follow-up (for progression-free survival): Abou-Alfa (2020): median 6.9 months (IQR: 2.8-10.9) Zhu (2021): not explicitly reported, the data cut-off date was 16 months after the data cut-ff date for Abou-Alfa (2020) Loss to follow-up or missing outcome data:* All patients were included in the analysis of overall survival and progression-free survival. For the safety analysis, 3 patients in the intervention group (3/124=2%) and 2 patients in the control group (2/61=3%) were excluded because they did not receive the study drug. *Quality of life at baseline, missing data*	*Overall survival* Overall survival Months, median (Abou-Alfa, 2020) I: 10.8 (95%CI: 7.7 to 17.6) C: 9.7 (95%CI: 4.8-12.1) HR 0.69 (95%CI: 0.44-1.10; p=0.060) Months, median (Zhu, 2021) I: 10.3 (95%CI 7.8 to 12.4) C: 7.5 (95%CI 4.8 to 11.1) HR 0.79 (95%CI: 0.56-1.12; p=0.09) Overall survival adjusted for the effect of placebo-ivosidenib crossover (Zhu, 2021) Months, median I: 10.3 (95%CI: 7.8 to 12.4) C: 5.1 (95%CI: 3.8 to 7.6) HR 0.49 (95%CI: 0.34 to 0.70; p<0.001) Overall survival at 6 months (Abou-Alfa, 2020) I: 67% (95%CI: 56-75) C: 59% (95%CI: 44-71)	Remarks: 43 patients crossed over from placebo to ivosidenib Abou-Alfa (2020) used a data cut-off date of January 31, 2019 while Zhu (2021) used a data cut-off date of May 31, 2020 Quality of life analyses were limited by small sample sizes as patients tended to have short treatment duration. Authors' conclusion: Abou-Alfa (2020): Ivosidenib therapy significantly improved progression-free survival and overall survival after adjusting for crossover, with a favourable safety profile, in patients with advanced, *IDH1*-mutant cholangiocarcinoma who had progressed on standard chemotherapy. This study shows the feasibility and clinical benefit of targeting a molecularly defined

	was provided by the funder. <u>Conflicts of interest:</u> An extensive list of potential conflicts of interests was reported. One author is consultant for Agios. Six authors received research grants or funding (to institution) from Agios. Eight authors are on advisory boards for Agios. One author received honoraria and travel and accommodation funding from Agios. Five authors are employees of and hold stock in Agios. One author is an employee of, hold stock in, and holds patents, royalties, and other intellectual property with Agios.	• life expectancy ≥ 3 months • ECOG performance status 0-1 • measurable lesion as defined by RECIST version 1.1 • adequate hematological, hepatic and renal function • patients who received previous local therapy were eligible provided measurable disease fell outside of the treatment field, or within the field but had shown ≥ 20% growth in tumor size since the post-treatment assessment <u>Exclusion criteria:</u> • patients who received systemic anticancer therapy or an investigational agent < 2 wks before day 1 (washout from previous immune-based			EORTC QLQ-C30 I: 11/124 (9%) / c: 9/61 (15%) EORTC-QLQ-BIL21 I: 17/24 (14%) / C: 10/61 (16%) *Quality of life at cycle 2 day 1, missing data* EORTC QLQ-C30 I: 51/113 (45%) / C: 32/52 (62%) EORTC-QLQ-BIL21 I: 47/107 (44%) / C: 32/51 (63%)	<u>Overall survival at 12 months (Zhu, 2021)</u> I: 43% (95%CI: 34 to 51) C: 36% (95%CI: 24 to 48) *Quality of life* <u>EORTC QLQ-C30 mean differences of ivosidenib versus placebo (cycle 2 day 1 and cycle 3 day 1) (Zhu, 2021)</u> *Global health status and functional subscales* Global health status/QoL: cycle 2: diff < 10 points cycle 3: diff < 10 points Physical functioning: cycle 2: diff ≥ 10 points (11.0 95%CI 4.23 to 17.73) cycle 3: diff ≥10 points (12.3 95%CI 3.85 to 20.78) Differences in favour of ivosidenib Social functioning: cycle 2: diff < 10 points cycle 3: diff < 10 points Role functioning: cycle 2: diff < 10 points cycle 3: diff < 10 points Cognitive functioning: cycle 2: diff < 10 points cycle 3: diff < 10 points Emotional functioning: cycle 2: diff ≥ 10 points	subgroup of cholangiocarcinoma and warrants tumor mutation profiling as a new standard of care in this heterogeneous disease. Zhu (2021): This randomized clinical trial found that ivosidenib was well tolerated and resulted in a favorable overall survival benefit vs placebo, despite a high rate of crossover. These data, coupled with supportive quality of life data and a tolerable safety profile, demonstrate the clinical benefit of ivosidenib for patients with advanced cholangiocarcinoma with *IDH1* mutation.

		anticancer therapy being 4 wks) • patients who received radiotherapy to metastatic sites of disease < 2 wks before day 1 • patients who undergone hepatic irradiation, chemoembolisation, and radiofrequency ablation less than 4 weeks before day 1 • any of the following comorbidities: active cardiac disease within 6 months before the start of study treatment; myocardial infarction, unstable angina or stroke; active hepatitis B or C viral infections; known positive HIV antibody results, or AIDS-related illness <u>N total at baseline:</u>*				cycle 3: diff ≥ 10 points Differences in favour of ivosidenib *Symptoms subscales* Fatigue Cycle 2: diff < 10 points Cycle 3: diff < 10 points Nausea and vomiting Cycle 2: diff < 10 points Cycle 3: diff < 10 points Pain Cycle 2: diff ≥ 10 points (-10.4 95%CI -20.18 to -0.52) Difference in favour of ivosidenib Cycle 3: diff < 10 points Dyspnea Cycle 2: diff ≥ 10 points Difference in favour of ivosidenib Cycle 3: diff < 10 points Insomnia Cycle 2: diff < 10 points Cycle 3: diff < 10 points Appetite loss Cycle 2: diff < 10 points Cycle 3: diff < 10 points Constipation Cycle 2: diff < 10 points Cycle 3: diff < 10 points Diarrhea Cycle 2: diff < 10 points Cycle 3: diff < 10 points	

		Randomized: n = 185 I: n = 124 C: n = 61 <u>Important characteristics:</u>* Age, median (range): I: 61 y (33-80) C: 63 y (40-83) Sex, n/N (%) male: I: 44/124 (35%) C: 24/61 (39%) Previous lines of therapy *One* I: 53% / 54% *Two* I: 47% / 46% Performance status *0* I: 49/124 (40%) C: 19/61 (31%) *1* I: 74/124 (60%) C: 41/61 (67%) *2* I: 0/124 (0%) C: 1/61 (2%) *3* I: 1/124 (1%) C: 0/61 (0%)				Financial difficulties Cycle 2: diff < 10 points Cycle 3: diff < 10 points <u>EORTC QLQ-BIL21 change scores between arms (baseline to cycle 2 day 1 and cycle 3 day 1) (Zhu, 2021)</u> Weight loss Cycle 2: diff < 10 points Cycle 3: diff < 10 points Drains Cycle 2: diff < 10 points Cycle 3: diff < 10 points Treatment side effects Cycle 2: diff < 10 points Cycle 3: diff < 10 points Anxiety Cycle 2: diff ≥ 10 points Difference in favour of ivosidenib Cycle 3: diff < 10 points Pain Cycle 2: diff < 10 points Cycle 3: diff < 10 points Tiredness Cycle 2: diff ≥ 10 points Difference in favour of ivosidenib Cycle 3: diff < 10 points Jaundice Cycle 2: diff < 10 points Cycle 3: diff < 10 points	

		Disease extent *Locally or regionally advanced* I: 9/124 (7%) C: 5/61 (8%) *Metastatic* I: 115/124 (93%) C: 56/61 (92%) Primary tumor site *Intrahepatic* I: 111/124 (90%) C: 58/61 (95%) *Extrahepatic* I: 1/124 (1%) C: 1/61 (2%) *Perihilar* I: 4/126 (3%) C: 0/61 (0%) *Unknown* I: 8/124 (6%) C: 2/61 (3%) Groups were comparable at baseline.				Eating Cycle 2: diff < 10 points Cycle 3: diff < 10 points *Progression-free survival* <u>Progression-free survival by assessment of the central independent radiology center (Abou-Alfa, 2020)</u> Months, median I: 2.7 (95%CI: 1.6 to 4.2) C: 1.4 (95%CI: 1.4 to 1.6) HR 0.37 (95%CI: 0.25 to 0.54; p<0.0001) <u>Progression-free survival at 6 months (Abou-Alfa, 2020)</u> I: 32% (95%CI: 23-42) C: 0% <u>Progression-free survival at 12 months (Abou-Alfa, 2020)</u> I: 22% (95%CI: 13-32) C: 0% *Toxicity* <u>Any grade ≥ 3 treatment-emergent adverse events * (Zhu, 2021)</u> <u>*Any*</u> I: 62/123 (50%) C: 22/59 (37%) <u>Treatment-emergent adverse events grade ≥ 3 reported in 5% or more of patients in a treatment group (Zhu, 2021)</u>	

						Ascites I: 11/123 (9%) / C: 4/59 (7%) *Anemia* I: 8/123 (7%) / C: 0/59 (0%) *Increased bilirubin level* I: 7/123 (6%) / C: 1/59 (2%) *Hyponatremia* I: 7/123 (6%) / C: 6/59 (10%) *Hypophosphatemia* I: 4/123 (3%) / C: 3/59 (5%) *Increased ALP level* I: 3/123 (2%) / C: 3/59 (5%)	
Demols (2020) (REACHIN trial)	Type of study: Multicenter, randomized, double-blind phase II trial Setting and country: 12 centers in Belgium Source of funding: This work was supported and sponsored (no grant number) by CUB Hôpital Erasme (Brussels, Belgium). Support from Bayer HealthCare (no grant number). Conflicts of interest: One author received travel support and fees for ad-board	Patients with locally advanced or metastatic biliary tract cancer who had disease progression after first-line gemcitabine and platinum-based chemotherapy Inclusion criteria: - Patients with histologically proven locally advanced unre-sectable or metastatic intrahepatic (IH), perihilar (PH), or extrahepatic cholangiocarcino ma or gallbladder tumor - Patients who had progressed after gemcitabine/plati	Regorafenib 160 mg once daily during 3 weeks of each 4-week cycle 3 weeks on / 1 week off and best supportive care (including biliary drainage, analgesics, antibiotics, steroids and antiemetics)	Placebo once daily 3 weeks on / 1 week off and best supportive care (including biliary drainage, analgesics, antibiotics, steroids and antiemetics)	Length of follow-up: Median 24 months Loss to follow-up or missing outcome data: All patients were included in the analysis of overall survival, progression-free survival, and safety.	Overall survival Months, median I: 5.3 (95%CI: 2.7 to 10.5) C: 5.1 (95%CI: 3.0 to 6.4) The hazard ratio should be interpreted with caution because the hazards did not appear proportional over time HR 0.77 (95%CI: 0.45-1.31) Progression-free survival Months, median I: 3.0 (95%CI: 2.3 to 4.9) C: 1.5 (95%CI: 1.2 to 2.0) HR 0.49 (95%CI: 0.29 to 0.81; p=0.004) Toxicity *Any grade ≥ 3 adverse event* I: 12/33 (36%) C: 8/33 (24%) p > 0.05 *Nausea/vomiting* I: 3/33 (9%) C: 2/33 (6%)	Remarks: Forty-three patients had available tumor samples for biomarker analysis. Only one FGFR2 fusion was found in the regorafenib arm. Of note, the patient with an FGFR2 fusion, and treated with regorafenib, had a PFS of 10.6 months. The patient with an FGFR2 fusion, treated with regor-afenib, had an OS of 26.1 months (after disease progression in this trial, he was included in a clinical trial and treated with pemigatinib). Authors' conclusions REACHIN is the first multicenter, randomized, placebo-controlled, phase II trial to show that regorafenib is active and significantly increases median PFS in patients with locally advanced/metastatic

	participations from Bayer. Another author received grants and fees from Bayer. All remaining authors have declared no conflicts of interest.	num-based chemotherapy (cisplatin or oxaliplatin, delivered in one or successive lines) were eligible. - age older than 18 years - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, - measurable disease (RECIST 1.1). <u>N total at baseline:</u> Randomized: N = 66 I: n = 33 / C: n = 33 <u>Important characteristics:</u> Age, median (range) I: 59 (35 to 83) C: 64 (38 to 78) Sex, n/N (%) male: I: 21/33 (63%) C: 19/33 (59%) Performance status				*Fatigue* I: 6/33 (18%) C: 3/33 9%) *Diarrhea* I: 1/33 (3%) C: 0/33 (0%) *Hypophosphatemia* I: 1/33 (3%) C: 0/33 (0%) *Hand foot skin reaction* I: 3/33 (9%) C: 0/33 (0%) *Mucositis* I: 1/33 (3%) C: 0/33 (0%) *Anorexia* I: 1/33 (3%) C: 1/33 (3%)	biliary tract tumors that progress after gemcitabine/platinum-based chemotherapy, whether in second or subsequent lines.

		0 I: 21/33 (64%) C: 15/33 (45%) *1* I: 12/33 (36%) C: 18/33 (55%) Primary tumor site *Intrahepatic* I: 23/33 (70%) C: 19/33 (58%) *Extrahepatic* I: 3/33 (9%) C: 6/33 (18%) *Gallbladder* I: 4/33 (12%) C: 5/33 (15%) *Perihilar* I: 3/33 (9%) C: 3/33 (9%) Groups were generally comparable at baseline.					
Lamarca (2021) (ABC-06 trial)	Type of study: Multicenter, randomized, open-label phase III trial Setting and country: 20 sites with expertise in	Patients with advanced biliary tract cancer who had disease progression on first-line treatment with cisplatin and gemcitabine Inclusion criteria:	Active symptom control* + folinic acid (L-folinic acid 175 mg or folinic acid 350 mg), fluorouracil (400 mg/m^2), and oxaliplatin (85 mg/m^2) (FOLFOX)	Active symptom control*	Length of follow-up: Median 21.7 months (IQR: 17.2 to 30.8) Loss to follow-up or missing outcome data: All patients were included in the analysis of overall survival, progression-free survival, and safety.	Overall survival Months, median I: 6.2 (95%CI: 5.4 to 7.6) C: 5.3 (95%CI: 4.1 to 5.8) HR 0.69 (95%CI: 0.50 to 0.97; p=0.031) (HR adjusted for platinum sensitivity, serum albumin concentration, and disease stage)	Definitions: * Active symptom control consisted of early identification and treatment of biliary-related complications and cancer-related symptom management; it could include (and was not limited to) the following as per requirements of individual

	managing biliary tract cancer in UK <u>Source of funding:</u> Cancer Research UK, StandUpToCancer, AMMF, and The Christie Charity, with additional funding from The Cholangiocarcinoma Foundation and the Conquer Cancer Foundation Young Investigator Award for translational research. The funders for this academic investigator-initiated study provided input in the form of peer review to ensure patient acceptability but had no role in study design in conception. The study sponsor provided regulatory and governance oversight with no direct involvement in design or data.	- age ≥ 18 y - histologically or cytologically verified locally advanced or metastatic biliary tract cancer (incl. cholangiocarcinoma, gallbladder carcinoma, and ampullary carcinoma) - documented radiological disease progression to previous first-line cisplatin and gemcitabine chemotherapy - ECOG performance status 0-1 - adequate hematological, renal and liver function - adequate biliary drainage, with no evidence of ongoing infection - life expectancy >3 months - all patients must be randomized and sites must ensure that patients allocated chemotherapy (control group) start treatment within 6 weeks of				<u>Subgroup analyses of overall survival</u> *Platinum sensitive* Yes: HR 0.81 (95%CI 0.47 to 1.40) No: HR 0.63 (95%CI 0.41 to 0.96) *Albumin* <35 g/L: HR 0.41 (95%CI 0.20 to 0.83) ≥35 g/L: HR 0.84 (95%CI 0.58 to 1.23) *Disease stage* Locally advanced: HR 0.73 (95%CI 0.32 to 1.67) Metastatic: HR 0.70 (95%CI 0.48 to 1.00) *Primary tumour site* Intrahepatic: HR 0.64 (95%CI 0.38 to 1.06) Extrahepatic: HR 0.84 (95%CI 0.45 to 1.57) Gallbladder and cystic duct: HR 0.56 (95%CI 0.27 to 1.17) Ampulla: HR 0.71 (95%CI 0.18 to 2.77) *ECOG performance status* 0: HR 0.85 (95%CI 0.32 to 1.08) 1: HR 0.73 (95%CI 0.49 to 0.97) <u>Progression-free survival</u> Months, median I: 4.0 (95%CI: 3.2 to 5.0) C: no data provided	patients: biliary drainage, antibiotics, analgesia, steroids, antiemetics, other palliative treatment for symptom control, palliative radiotherapy (e.g. for painful bone metastases), and transfusion of blood products. <u>Remarks:</u> Data on quality of life (EORTC QLQ-30, EORTC QLQ-BIL21 and EQ-5D)-and health economics will be reported separately. 11 patients (7%) had ampullary cancer, which is outside the scope of this literature summary <u>Authors conclusion:</u> The addition of FOLFOX to active symptom control improved median overall survival in patients with advanced biliary tract cancer after progression on cisplatin and gemcitabine, with a clinically meaningful increase in 6-month and 12-month overall survival rates. To our knowledge, this trial is the first prospective, randomized study providing reliable, high-quality evidence to allow an informed discussion with patients of the potential benefits and risks from second-line FOLFOX

	Conflicts of interest: An extensive list of potential conflicts of interest was reported.	radiological progression - patients who had been started on first-line cisplatin and gemcitabine for whom the cisplatin was stopped due to toxicity (with continuation of gemcitabine) were eligible. Exclusion criteria: - any other form of first-line systemic chemotherapy or additional line of first-line chemotherapy (incl. rechallenge with cisplatin and gemcitabine) was not allowed - incomplete recovery from previous therapy (incl. ongoing neuropathy of grade >1 from cisplatin) - clinical evidence of metastatic disease to brain - clinically significant cardiovascular disease				**Safety** Toxicity grade ≥ 3 (regardless of causality) *Any* I: 56/81 (69%) C: 42/81 (52%) p = 0.0363 *Toxicity grade ≥ 3 treatment-emergent adverse events reported in 5% or more of patients in a treatment group* *Neutropenia* I: 10/81 (12%) C: 1/81 (1%) *Fatigue/lethargy* I: 15/81 (19%) C: 6/81 (7%) *Infection* I: 15/81 (19%) C: 5/81 (6%) *Biliary event* I: 16/81 (20%) C: 17/81 (21%) *Hypertension* I: 4/81 (5%) C: 1/81 (1%) *Vomiting* I: 3/81 (4%) C: 4/81 (5%) *Anorexia* I: 1/81 (1%) C: 6/81 (7%)	chemotherapy in advanced biliary tract cancer. Based on these findings, FOLFOX should become standard-of-care chemotherapy in second-line treatment for advanced biliary tract cancer and the reference regimen for further clinical trials.

		N total at baseline: Randomized: N = 162 I: n = 81 C: n = 81 Important characteristics: Age, median (IQR): I: 65 y (59 to 72) C: 65 y (59 to 72) Sex, n/N (%) male: I: 43/81 (53%) C: 37/81 (46%) Performance status *0* I: 25/81 (31%) C: 28/81 (35%) *1* I: 55/81 (68%) C: 52/81 (64%) Disease stage *Locally advanced* I: 14/81 (17%) C: 15/81 (19%) *Metastatic* I: 67/81 (83%) C: 66/81 (81%) Primary tumor site *Intrahepatic*				*Pain* I: 8/81 (10%) C: 6/81 (7%) *Thromboembolic event* I: 0/81 (0%) C: 4/81 (5%)	

		I: 34/81 (42%) C: 38/81 (47%) *Extrahepatic* I: 26/81 (32%) C: 19/81 (23%) *Gallbladder* I: 17/81 (21%) C: 17/81 (21%) *Ampulla* I: 4/81 (5%) C: 7/81 (9%) Groups were generally comparable at baseline.					

Risk of bias assessment

Risk of bias assessment of intervention studies (randomized controlled trials)

Study reference	**Was the allocation sequence adequately generated?**[a] Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?**[b] Definitely yes Probably yes Probably no Definitely no	**Was knowledge of the allocated interventions adequately prevented?**[c] **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?**[d] Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?**[e] Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?**[f] Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure**[g] LOW SOME CONCERNS HIGH
Abou-Alfa (2020), Zhu (2021) (ClarIDHy trial)	Definitely yes; Randomisation into the two treatment groups was generated by an independent statistical group.	Definitely yes; Patients were randomly assigned (2:1) to ivosidenib or matched placebo, with a block size of 6, and stratified by number of previous systemic	Definitely yes; Ivosidenib and placebo were packaged and labelled identically to ensure that study personnel remained masked to treatment assignment. Patients, investigators and their teams, and designated individuals from the	Definitely yes; (for overall survival, progression-free survival, toxicity) All randomized patients were included in the intention to treat analysis for overall survival and progression-free survival. For the safety analysis,	Definitely yes; All outcome measures described in the trial protocol are reported in these articles, except for health economic (EQ-5D-5L) findings. However, these results will be reported elsewhere.	Definitely no; The funder (Agios Pharmaceuticals) had a role in study design, data collection, data analysis, and data interpretation. Medical writing support was provided by the funder. Several authors are employee of, hold stock in, or hold patents, royalties,	SOME CONCERNS (overall survival, quality of life, progression-free survival, toxicity) The study was designed and data analyzed by the funder in collaboration with the investigators. Several authors are employee of, hold stock in, or hold patents, royalties, and other

		treatment regimens for advanced disease. Randomisation into the two treatment groups was implemented by an interactive web-based response system.	sponsor were masked to study treatment until disease progression as assessed by the investigator. On the basis of investigator-confirmed radiographic progression, unmasking was permitted and eligible patients receiving placebo were permitted to receive open-label ivosidenib.	3 patients in the intervention group (3/124=2%) and 2 patients in the control group (2/61=3%) were excluded because they did not receive the study drug. Definitely no; (quality of life) For quality of life, a considerable amount of data was missing (9% to 16% at baseline, 44% to 63% at cycle 2 day 1)		and other intellectual property with Agios Pharmaceuticals. 43 out of 61 patients in the placebo group crossed over to ivosidenib	intellectual property with Agios Pharmaceuticals.
Demols (2020) (REACHIN trial)	Definitely yes; Eligible patients were randomly assigned (1:1) using a computer-generated randomization list (pre-allocated block design, no stratification factors).	Probably yes; Study medication was labelled with a unique preprinted label including vial and batch number.	Definitely yes; Pharmacists in each center were unblinded and managed the study drug supply. To maintain blinding, study medication was labelled with a unique preprinted label including vial and batch number.	Definitely yes; All randomized patients were included in the intention to treat analysis for overall survival, progression-free survival, and safety.	Definitely yes; All outcome measures described in the trial register are reported in this article.	Definitely no; This study was funded by Bayer HealthCare. Two authors received travel support, grants and fees (for ad-board participations) from Bayer.	SOME CONCERNS (overall survival, progression-free survival, toxicity) The study was funded by Bayer HealthCare. Two authors received travel support, grants and fees (for ad-board participations) from Bayer.
Lamarca (2021) (ABC-06 trial)	Definitely yes; Patients were randomly assigned (1:1) to active symptom control plus FOLFOX or active symptom control alone. Researchers contacted a central telephone number	Definitely yes; Researchers contacted a central telephone number whereupon Clinical Trials Unit (CTU) staff used a computer system employing a minimisation algorithm over	Definitely no; Open-label study with no masking	Definitely yes; All randomized patients were included in the intention to treat analysis for overall survival and safety. For progression-free survival, all patients randomized to the intervention group were	Definitely yes; All outcome measures described in the study protocol are reported in the article, except for quality of life and health economics. These outcomes will be reported separately.	Probably yes;	SOME CONCERNS (overall survival, progression-free survival, toxicity) This is an open-label phase III study

	whereupon Clinical Trials Unit (CTU) staff used a computer system employing a minimisation algorithm over the margins of three factors to determine the allocation. Allocations were made with a probability of 0.75 to the group that would yield improved balance or 0.5 if balance scores were tied.	the margins of three factors to determine the allocation. Allocations were revealed to the CTU staff member only after all the participant details had been committed to the system. The allocation was then relayed verbally to the caller and an automated confirmation e-mail was sent to the recruiting site.		included in the analysis. Progression-free survival was not reported for the control group			

[a] Randomization: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
[b] Allocation concealment: refers to the protection (blinding) of the randomization process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomization (performed at a site remote from trial location). Inadequate procedures are all procedures based on inadequate randomization procedures or open allocation schedules.
[c] Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments, but this should not affect the risk of bias judgement. Blinding of those assessing and collecting outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment or data collection (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is usually not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary. Finally, data analysts should be blinded to patient assignment to prevents that knowledge of patient assignment influences data analysis.
[d] If the percentage of patients lost to follow-up or the percentage of missing outcome data is large, or differs between treatment groups, or the reasons for loss to follow-up or missing outcome data differ between treatment groups, bias is likely unless the proportion of missing outcomes compared with observed event risk is not enough to have an important impact on the intervention effect estimate or appropriate imputation methods have been used.
[e] Results of all predefined outcome measures should be reported; if the protocol is available (in publication or trial registry), then outcomes in the protocol and published report can be compared; if not, outcomes listed in the methods section of an article can be compared with those whose results are reported.
[f] Problems may include: a potential source of bias related to the specific study design used (e.g. lead-time bias or survivor bias); trial stopped early due to some data-dependent process (including formal stopping rules); relevant baseline imbalance between intervention groups; claims of fraudulent behavior; deviations from intention-to-treat (ITT) analysis; (the role of the) funding body. Note: The principles of an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.
[g] Overall judgement of risk of bias per study and per outcome measure, including predicted direction of bias (e.g. favors experimental, or favors comparator). Note: the decision to downgrade the certainty of the evidence for a particular outcome measure is taken based on the body of evidence, i.e. considering potential bias and its impact on the certainty of the evidence in all included studies reporting on the outcome.

Implementatieplan bij module 12 Palliatieve systemische behandeling na de 1e lijn

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen
Bepaal met behulp van Samen Beslissen of tweedelijns behandeling gestart dient te worden.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn	Wetenschappelijke verenigingen	
Bespreek de mogelijkheid van actieve symptoombestrijding indien er besloten wordt geen tumorgerichte tweedelijns behandeling te starten. Actieve symptoombestrijding zoals in de ABC-06 studie bestond uit elke 4 weken fysieke controle met leverwaarden en onder andere eventuele behandeling enzymsuppletie, maaguitgangstenose, galwegobstructie en cholangiosepsis.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn	Wetenschappelijke verenigingen	
Bespreek bij wens voor tweedelijns palliatieve systeemtherapie de behandeling met FOLFOX en bespreek ook dat deze winst gemiddeld beperkt is.	< 1 jaar	Geen	Bekendheid met richtlijn	Geen	Publicatie richtlijn	Wetenschappelijke verenigingen	
Overweeg mismatch repair eiwitten te bepalen en simultaan pan-TRK immunokleuring te doen (NB alleen fusie NTRK als pan-TRK kleuring positief) indien een patient in aanmerking komt voor een reguliere behandeling in tweedelijn, alhoewel dit zeldzaam voorkomt. Behandel in geval van NTRK fusie met larotrectinib en in geval van	1-3 jaar	Toename kosten door bepaling	Bekendheid met richtlijn Financiering voor bepaling	Kosten, bepalingstechniek beschikbaar?	Publicatie richtlijn Publicatie MKNT lijsten	Wetenschappelijke verenigingen, VWS	

dMMR/MSIhigh met pembrolizumab of nivolumab. Overleg vóór de start van tweedelijns FOLFOX met een centrum met voldoende expertise welke aanvullende bepalingen (immuunhistochemie/moleculaire markers) en welke behandelingen in studieverband voorhanden zijn.	1-3 jaar	Toename kosten door bepalingen	Bekendheid met richtlijn Overleg lijnen met expertcentra	Overleglijnen niet bekend, expertcentra niet bekend	Publicatie MKNT lijsten		

Table of excluded studies

Author and year	Reason for exclusion
Systematic reviews	
Kamarajah 2020	Wrong intervention: neoadjuvant treatment
Belkouz 2019	Wrong comparison: biomarker expression
Lamarca 2019	Wrong study design: post-hoc analyses
Li 2019	Wrong study design: systematic review and network meta-analyse of RCTs and retrospective studies, mostly focused on first-line treatment
Javle 2019	Wrong study design: narrative review
Ying 2019	Wrong study design: systematic review of retrospective studies
Hakeem 2019	Wrong intervention: neoadjuvant treatment
Zhang 2019	Wrong study design: case report and narrative review
Zheng 2019	Wrong intervention: first-line treatment
Cai 2018	Wrong intervention: first-line treatment
Zhuang 2017	Wrong intervention: first-line treatment
Sun 2017	Wrong intervention: first-line treatment
Zhao 2016	Wrong intervention: first-line treatment
Sicklick 2016	Wrong study design: narrative review
Vogel 2018	Wrong study design: original study focused on first-line treatment
Chen 2016	Wrong intervention: first-line treatment
Moriwaki 2016	Wrong intervention: first-line treatment
Simo 2016	Wrong intervention: not focused on second-line treatment
Tampellini 2016	Wrong study design: narrative review
Park 2015	Wrong intervention: first-line treatment
Boehm 2015	Wrong intervention: not focused on systemic treatment
Liu 2014	Wrong intervention: first-line treatment
Valle 2014	Wrong intervention: first-line treatment
Zhu 2014	Wrong intervention: adjuvant treatment
Eckel 2014	Wrong intervention: first-line treatment
Fiteni 2014	Wrong intervention: first-line treatment
Grendar 2014	Wrong intervention: neoadjuvant treatment
Lamarca 2014	Wrong study design: no RCTs included in review
Yang 2013	Wrong intervention: first-line treatment
Sun 2013	Wrong intervention: first-line treatment
Roth 2012	Wrong study design: cost-effectiveness study
RCTs	
Abou-Alfa 2020	Wrong study design: not an RCT
Davis 2018	Wrong study design: not an RCT
Demols 2019	Wrong publication type: abstract only
Javle 2018	Wrong study design: not an RCT
Kataria 2019	Wrong publication type: abstract only
Kim (2020)	Wrong comparison: two different types of second-line treatment
Kim 2019	Wrong intervention: first-line treatment
Lamarca 2020	Wrong study design: not an RCT (post-hoc analysis)
Morizane 2019	Wrong intervention: first-line treatment
Yoon 2018	Wrong publication type: abstract only
Zheng 2018	Wrong comparison: two different types of second-line treatment
Chiang 2018	Wrong study design: not an RCT
Feng 2020	Wrong study design: not an RCT
Harding 2019	Wrong publication type: abstract only

Hollebecque 2018	Wrong study design: not an RCT
Ikeda 2018	Wrong study design: not an RCT
Iyer 2018	Wrong study design: not an RCT
Javle 2018	Wrong publication type: abstract only
Jensen 2020	Wrong study design: not an RCT
Kim 2019	Wrong study design: not an RCT
Kim 2018	Wrong study design: not an RCT
Kim 2020	Wrong study design: not an RCT
Kim 2020	Wrong study design: not an RCT
Klein 2020	Wrong study design: not an RCT
Larsen 2018	Wrong study design: not an RCT
Markussen 2020	Wrong intervention: first-line treatment
Okano 2020	Wrong study design: not an RCT
Perkhofer 2019	Wrong intervention: first-line treatment
Sahai 2018	Wrong intervention: first-line treatment
Sgouros 2020	Wrong study design: not an RCT
Shroff 2019	Wrong study design: not an RCT
Subbiah 2020	Wrong study design: not an RCT
Sun 2019	Wrong study design: not an RCT
Vogel 2018	Wrong intervention: first-line treatment
Yoo 2018	Wrong intervention: first-line treatment
Javle 2019	Wrong intervention: first-line treatment
Yang 2020	Wrong intervention: systemic treatment and locoregional treatment

Literature search strategy for systematic reviews

Embase (via Embase.com)

'biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR 'bile duct') NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ab,ti,kw AND [english]/lim AND [2012-2019]/py NOT 'conference abstract':it NOT ([animals]/lim NOT [humans]/lim) AND ('systematic review'/exp OR 'meta analysis'/exp OR (((systematic*) NEAR/3 (review)) OR meta-analy* OR metaanaly*):ab,ti,kw)

481 hits

Medline (via OVID)

exp Gallbladder Neoplasms/ or exp biliary tract neoplasms/ or exp bile duct neoplasms/ or exp cholangiocarcinoma/ or exp klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile duct) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplasm* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ab,ti,kf.
AND english.la.
AND (2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020)
NOT (exp animals/ NOT humans/)
AND (Systematic Review/ OR Meta-Analysis/ OR (((systematic*) ADJ3 (review)) OR meta-analy* OR metaanaly*).ab,ti,kf.)

251 hits

Literature search strategy for RCTs

Embase (via Embase.com)

('biliary tract tumor'/exp/mj OR 'gallbladder carcinoma'/exp/mj OR 'klatskin tumor'/exp/mj OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin*):ti,kw) AND [english]/lim AND [2015-2020]/py NOT 'conference abstract':it NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) AND (('clinical trial'/exp OR (trial):ab,ti,kw) OR [clinical trial number]/lim)

766 hits

Medline (via OVID)

(exp *Gallbladder Neoplasms/ or exp *biliary tract neoplasms/ or exp *bile duct neoplasms/ or exp *cholangiocarcinoma/ or exp *klatskin tumor/ OR (((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) ADJ6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin).ti,kf.) AND english.la. AND 2015:2020.(sa_year). NOT (exp animals/ NOT humans/) AND ((Clinical Trial/ OR (trial).ab,ti,kf.) OR clinicaltrials.si.)

422 hits

Cochrane Central Register of Controlled Trials (via Wiley)

((((gallbladder* OR gall-bladder* OR biliary OR bile-duct*) NEAR/6 (carcinom* OR cancer* OR tumor* OR tumour* OR neoplas* OR malign* OR oncolog*)) OR cholangiocarcinom* OR klatskin):ti)

643 hits

Kennislacunes

Hoofdstuk	nr	Moduletitel	Kennislacunes
Diagnostiek	6	Cross-sectionele beeldvorming	Wat is de diagnostische test accuratesse, de kosteneffectiviteit en het effect op overleving van een aanvullende MRI en wat is de impact op het beleid van de patient met een verdenking op een galblaas- of cholangiocarcinoom wanneer MRI wordt toegevoegd aan de diagnostische work-up? Wat is de invloed op overleving, verandering in beleid en kosteneffectiviteit van een additionale MRI scan bij de stadiëring van patiënten met (een verdenking op) galblaas- of galwegcarcinoom?
Behandeling	7	Locoregionale behandeling met TACE of SIRT voor iCCA	Is de overleving beter na aanvullende locoregionale behandeling met TACE of SIRT bij patiënten met een niet-resectabel iCCA? Is de overleving beter na aanvullende locoregionale behandeling met HAIP chemotherapie met bijvoorbeeld floxuridine bij patiënten met een niet-resectabel iCCA? Wat is de optimale timing van locoregionale behandeling van iCCA; voor, tijdens, of na systemische behandeling?
Behandeling	8	Preoperatieve vena porta embolisatie	Wat is het effect van VPE op postoperatief leverfalen en mortaliteit in patiënten die gepland zijn voor een resectie voor galwegkanker? Wat is de rol en toegevoegde waarde van het toevoegen van embolisatie van levervenen “veneuze deprivatie” aan VPE? Wat is de toegevoegde waarde van lever scintigrafie ten opzichte van volumetrie om de kans op postoperatief leverfalen en mortaliteit te voorspellen? Hoe kan betrouwbaar voorspeld worden welke patiënt onvoldoende hypertrofie zal hebben na alleen PVE en dus een aanvullende procedure (ALPPS, DVE) behoeft?
Behandeling	9	Indicatie resectie	Wat is het effect op overleving van inductietherapie bij patiënten met lokaal uitgebreid galweg- of galblaaskanker ten opzichte van direct opereren of palliatieve systemische therapie? Wat is het effect op overleving van neoadjuvante therapie bij patiënten met resectabel galweg- of galblaaskanker ten opzichte van direct opereren?
Behandeling	10	Adjuvante systemische behandeling	Omdat reeds verrichte gerandomiseerde studies geen of weinig winst hebben laten zien, is er behoefte aan meer effectieve adjuvante behandeling. De recent gecompleteerde ACTICCA-1 studie zal hier misschien een antwoord op geven. Eerdere gerandomiseerde studies zijn verricht in alle subtypes van het galweg- en galblaascarcinoom. Er is behoefte aan een calculator om voor individuele patiënten de verwachte verbetering in overleving van adjuvante behandeling te kunnen berekenen.
Behandeling	11	Palliatieve systemische behandeling in de 1e lijn	Er is behoefte aan meer onderzoek naar predictieve maar ook prognostische biomarkers zodat beter voorspeld en dus voorgelicht kan worden voor wie welke behandeling het meest effectief is in de 1e lijn.

Behandeling	12	Palliatieve systemische behandeling na de 1e lijn	Wat is de effectiviteit van doelgerichte therapie in de 1e en 2e lijns behandeling van patienten met een lokaal gevorderd of gemetastaseerd galweg- of galblaascarcinoom? Wat zijn prognostische factoren voor biliaire tumoren?

Implementatieplan

Inleiding
Dit plan is opgesteld ter bevordering van de implementatie van de richtlijn Galweg- en galblaascarcinoom. Voor het opstellen van dit plan is een inventarisatie gedaan van de mogelijk bevorderende en belemmerende factoren voor het toepassen en naleven van de aanbevelingen. Daarbij heeft de richtlijnwerkgroep een advies uitgebracht over het tijdspad voor implementatie, de daarvoor benodigde randvoorwaarden en de acties die voor verschillende partijen ondernomen dienen te worden.

Werkwijze
De werkgroep heeft per aanbeveling geïnventariseerd:
- per wanneer de aanbeveling overal geïmplementeerd moet kunnen zijn;
- de verwachtte impact van implementatie van de aanbeveling op de zorgkosten;
- randvoorwaarden om de aanbeveling te kunnen implementeren;
- mogelijk barrières om de aanbeveling te kunnen implementeren;
- mogelijke acties om de implementatie van de aanbeveling te bevorderen;
- verantwoordelijke partij voor de te ondernemen acties.

Voor iedere aanbevelingen is nagedacht over de hierboven genoemde punten. Echter niet voor iedere aanbeveling kon ieder punt worden beantwoord. Er kan een onderscheid worden gemaakt tussen “sterk geformuleerde aanbevelingen” en “zwak geformuleerde aanbevelingen”. In het eerste geval doet de richtlijncommissie een duidelijke uitspraak over iets dat zeker wel of zeker niet gedaan moet worden. In het tweede geval wordt de aanbeveling minder zeker gesteld (bijvoorbeeld “Overweeg om …”) en wordt dus meer ruimte gelaten voor alternatieve opties. Voor “sterk geformuleerde aanbevelingen” zijn bovengenoemde punten in principe meer uitgewerkt dan voor de “zwak geformuleerde aanbevelingen”. Bij elke module is onderstaande tabel opgenomen.

Aanbeveling	Tijdspad voor implementatie: < 1 jaar, 1 tot 3 jaar of > 3 jaar	Verwacht effect op kosten	Randvoorwaarden voor implementatie (binnen aangegeven tijdspad)	Mogelijke barrières voor implementatie[1]	Te ondernemen acties voor implementatie[2]	Verantwoordelijken voor acties[3]	Overige opmerkingen

[1] Barrières kunnen zich bevinden op het niveau van de professional, op het niveau van de organisatie (het ziekenhuis) of op het niveau van het systeem (buiten het ziekenhuis). Denk bijvoorbeeld aan onenigheid in het land met betrekking tot de aanbeveling, onvoldoende motivatie of kennis bij de specialist, onvoldoende faciliteiten of personeel, nodige concentratie van zorg, kosten, slechte samenwerking tussen disciplines, nodige taakherschikking, et cetera.
[2] Denk aan acties die noodzakelijk zijn voor implementatie, maar ook acties die mogelijk zijn om de implementatie te bevorderen. Denk bijvoorbeeld aan controleren aanbeveling tijdens kwaliteitsvisitatie, publicatie van de richtlijn, ontwikkelen van implementatietools, informeren van ziekenhuisbestuurders, regelen van goede vergoeding voor een bepaald type behandeling, maken van samenwerkingsafspraken.

[3] Wie de verantwoordelijkheden draagt voor implementatie van de aanbevelingen, zal tevens afhankelijk zijn van het niveau waarop zich barrières bevinden. Barrières op het niveau van de professional zullen vaak opgelost moeten worden door de beroepsvereniging. Barrières op het niveau van de organisatie zullen vaak onder verantwoordelijkheid van de ziekenhuisbestuurders vallen. Bij het oplossen van barrières op het niveau van het systeem zijn ook andere partijen, zoals de NZA en zorgverzekeraars, van belang. Echter, aangezien de richtlijn vaak enkel wordt geautoriseerd door de (participerende) wetenschappelijke verenigingen is het aan de wetenschappelijke verenigingen om deze problemen bij de andere partijen aan te kaarten.

Implementatietermijnen
Voor "sterk geformuleerde aanbevelingen" geldt dat zij zo spoedig mogelijk geïmplementeerd dienen te worden. Voor de meeste "sterk geformuleerde aanbevelingen" betekent dat dat zij komend jaar direct geïmplementeerd moeten worden en dat per 2025 dus iedereen aan deze aanbevelingen dient te voldoen.

Aanbevelingen

Module 1 Meerwaarde PET bij biliaire tumoren

Aanbeveling-1

Verricht niet standaard een 18F-FDG-PET-scan bij de stadiëring van patiënten met galblaas- of galwegkanker.

Aanbeveling-2

Overweeg wél een 18F-FDG-PET-scan bij patiënten met: • een grote kans op afstandsmetastasen • een bovengemiddeld operatierisico

Module 2 Preoperatieve galwegdrainage

Overweeg de endoscopische benadering als eerste keus in de galwegdrainage bij patiënten met een (verdenking) resectabel perihilair cholangiocarcinoom afhankelijk van beschikbaarheid en expertise. Indien de endoscopische benadering niet succesvol is, is de percutane benadering te overwegen. Overleg bij een (verdenking) resectabele tumor welke galwegen de voorkeur hebben om te draineren met het oog op een operatie.

Module 3 Verslag en aanvraag pathologie

Aanbeveling-1

Klinische gegevens Vermeld als klinisch aanvrager bij galwegtumoren de volgende items op het pathologie-aanvraagformulier: • Aard van de ingreep/type operatie.

- Meegereserceerde structuren/organen (eventueel met markering).
- Lokalisatie tumor.
- Eventuele voorbehandeling (neo-adjuvante therapie, anders).
- Relevante voorgeschiedenis (inclusief familiaire belasting).

Aanbeveling-2

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

Indien maligniteit aanwezig:
Vermeld voor alle oncologische resecties van de galwegen en galblaas in ieder geval de volgende items in het pathologie verslag, indien maligniteit aanwezig:

Macroscopie:
- Beschrijving van de resectie: welke organen, afmetingen van het preparaat.
- Maximale tumorgrootte en lokalisatie/uitbreiding/ eventueel ingroei in aangrenzende structuren.
- Macroscopie van de tumor (aspect, groeiwijze).
- Veranderingen in aangrenzend weefsel (bijvoorbeeld levercirrose, steatose et cetera).
- Aanwezigheid precursorlesies (bijvoorbeeld Intraductale papillaire biliaire neoplasie, IPNB).
- Minimale marges ten opzichte van relevante resectie- en dissectievlakken (zie beschrijving per subtype).

Microscopie:
- Tumordifferentiatie: goed, matig, slecht.
- Subtype (cf WHO 5th edition):
    - Adenocarcinoom: *pancreatobiliair, intestinaal, mucineus, heldercellig, zegelringcelcarcinoom, adenosquameus carcinoom*.
    - Anders: zoals neuro-endocrien (groot- versus kleincellig subtype), mixed neuroendocrine-non-neuroendocrine (MINEN), plaveiselcelcarcinoom, sarcomatoid carcinoom, ongedifferentieerd carcinoom.
    - Eventueel onderliggende ziekten van lever en/of galwegen.

- Aanwezigheid en afmeting eventuele precursor lesies (iCCA, pCCA en dCCA), inclusief eventuele betrokkenheid resectievlak van precursorlesie:
    - Intraductale Papillaire Biliaire Neoplasie (IPBN).
    - Biliaire In Situ Neoplasia (Bil-IN).
    - Mucineus cystadenoom met invasieve component.

  NB. Precursor lesies van de galblaas: Bil-IN, intracholecystic papillary neoplasm en pyloric gland adenoom

  NB. Waar van toepassing moeten de grootte en de marges ten opzichte van de snijvlakken van invasieve component separaat van de in situ lesie worden vermeld in het verslag.

- Lymfvatinvasie.
- Veneuze invasie.
- Perineurale groei.

- Totaal aantal lymfeklieren en aantal met metastase (inclusief station, indien mogelijk/gemarkeerd); eventueel extranodale groei. NB. voor adequate stagering is een goed gedefinieerd/beschreven kliertoilet en markering van locatie van klieren aan te bevelen.
- Radicaliteit, inclusief R-status (conform de definities ICCR (Burt, 2020)): R0 = geen residuale tumor (marge ≥ 1 mm), R1 = microscopische residuale tumor (marge < 1mm), R2 = macroscopische residuale tumor (R-2 is een klinische diagnose, gesteund door pathologisch onderzoek van de marge aan de patiënt zijde, met andere woorden dit kan alleen de chirurg interpreteren).

Indien geen maligniteit kan worden aangetoond:
Als er in resectiepreparaat geen maligniteit kan worden aangetoond (na uitgebreid/volledig insluiten), dan moeten de overige gevonden afwijkingen in het verslag worden vermeld (bijvoorbeeld ontsteking, IgG4 gerelateerde ziekte et cetera).

Aanbeveling-3

Specifiek bij een distaal cholangiocarcinoom (dCCA)

Relevante marges:
Vermeld voor een oncologische resectie van een distaal cholangiocarcinoom de volgende aanvullende items in het pathologie verslag, waar van toepassing:
- Pancreasresectievlak.
- Common bile duct (CBD).
- Arteria Mesenterica Superior.
- Vena Mesenterica Superior/Vena Porta.
- Proximaal snijvlak (maag/duodenum).
- Distaal snijvlak (duodenum/jejenum).
- Posterieure vlak.

NB. Relatie met anterieure snijvlak moet worden vermeld, waarbij serosale ingroei relevant is (betreft geen chirurgisch snijvlak)

T stadium:
- pTX: tumor niet te beoordelen.
- pT0: geen tumor identificeerbaar.
- pTis: carcinoma in situ.
- pT1: tumor met groei in/door wand galweg en invasie diepte < 5mm.
- pT2: tumor met groei in/door wand galweg en invasie diepte 5 tot -12 mm.
- pT3: tumor met groei in/door wand galweg en invasie diepte > 12 mm.
- pT4: tumor met ingroei in truncus coeliacus, arteria mesenterica superior, en/ arteria hepatica communis.

N stadium:
- pN0: geen positieve regionale lymfeklieren.
- pN1: metastasen in 1 tot 3 regionale lymfeklieren.
- pN2: metastasen in 4 of meer regionale lymfeklieren.

Aanbeveling-4

Specifiek bij een perihilair cholangiocarcinoom (pCCA)

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

Mogelijke relevante marges (bij hemihepatectomie in overleg met operateur, met name voor wat betreft periductale weke delen vlak):
- Common bile duct (CBD).
- Ductus hepaticus.
- Vena porta.
- Arteria hepatica.
- Leverparenchymresectievlak.
- Periductale weke delen dissectievlak (radiale marge) bij hilus (zie verantwoording literatuur en klinische relevantie).

T stadium:
- pTX: tumor niet te beoordelen.
- pT0: geen tumor identificeerbaar.
- pTis: carcinoma in situ.
- pT1: tumor beperkt tot galwegwand (tot muscularis).
- pT2: tumorgroei door galwegwand heen:
  - pT2a: ingroei in aangrenzend vet.
  - pT2b: ingroei in leverparenchym.
- pT3: tumoringroei in ipsilaterale aftakking vena porta of arteria hepatica.
- pT4: tumoringroei in hoofdstam vena porta of aftakkingen (bilateraal); ingroei in arteria hepatica communis; ipsilaterale (second order) aftakkingen biliaire arteriele plexus met contralaterale vena porta of arteria hepatica betrokkenheid.

N stadium:
- pNX: niet te evalueren.
- pN0: geen positieve regionale lymfeklieren.
- pN1: metastasen in 1 tot 3 regionale lymfeklieren.
- pN2: metastasen in 4 of meer regionale lymfeklieren.

Regionale lymfeklieren zijn de klieren langs de ductus cysticus, bij hilus, common bile duct, vena porta, arteria hepatica communis en posterior pancreatoduodenaal: deze stations in het verslag benoemen, indien mogelijk (en waar van toepassing gemarkeerd ingezonden).

Aanbeveling-5

Specifiek bij een intrahepatisch cholangiocarcinoom (iCCA)
Vermeld voor een oncologische resectie van een intrahepatisch cholangiocarcinoom de volgende aanvullende items in het pathologie verslag, waar van toepassing:

Relevante marges:
- Leverparenchym.

Indien van toepassing (bijvoorbeeld bij hemihepatectomie):
- Common bile duct (CBD).
- Ductus hepaticus.
- Vena porta.
- Arteria hepatica.

- Periductale weke delen dissectievlak (radiale marge) bij hilus.

T stadium:
- pTX: tumor niet te beoordelen.
- pT0: geen tumor identificeerbaar.
- pTis: carcinoma in situ.
- pT1: Solitaire tumor zonder vaso-invasie:
  - pT1a: <= 5cm.
  - pT1b: > 5 cm.
- pT2: Solitaire tumor met vaso-invasie óf meerdere tumoren (met of zonder vaso-invasie).
- pT3: Tumoringroei door viscerale peritoneum.
- pT4: directe tumoringroei in extrahepatische structuren.

Het intrahepatisch cholangiocarcinoom kan worden onderscheiden in zogenaamde “small duct” en “large duct” types. In zeldzame gevallen (2 tot 5%) kan er sprake zijn van gecombineerd cholangiocarcinoom-hepatocellulair carcinoom. Deze subtypes zijn potentieel klinisch relevant en het verdient aanbeveling om het subtype iCCA in het verslag te benoemen (Kendall, 2019).

Aanbeveling-6

Specifiek bij een galblaascarcinoom
Vermeld voor een oncologische resectie van een galblaascarcinoom de volgende aanvullende items in het pathologie verslag:
NB. Macroscopisch beschrijven:
- aan welke zijde tumor groeit: leverbed zijde of serosale zijde (zodat dit ook microscopisch te bevestigen is). Dit is relevant voor onderscheid stadium 2a/2b en bij stadium 2b is aanvullende leverbed resectie geïndiceerd)
- Lokalisatie tumor: fundus, hals, corpus et cetera.

Relevante marges:
- Ductus cysticus snijvlak.
- Leverbedresectievlak.

T stadium:
- pTX: tumor niet te beoordelen.
- pT0: geen tumor identificeerbaar.
- pTis: carcinoma in situ.
- pT1: tumor ingroei in lamina propria of muscularis.
- pT2: tumorgroei door muscularis in perimusculaire weefsel:
  - pT2a: ingroei in perimusculaire weke delen aan peritoneale zijde.
  - pT2b: ingroei in perimusculaire weke delen, grenzend aan leverparenchym zonder ingroei in lever.
- pT3: tumoringroei in leverparenchym, serosa of ander orgaan (maag, duodenum, colon, pancreas, omentum, extrahepatische galwegen).
- pT4: tumoringroei in hoofdstam vena porta of arteria hepatica of ingroei in twee of meer extrahepatische organen/structuren.

N stadium:

- pNX: niet te evalueren.
- pN0: geen positieve regionale lymfeklieren.
- pN1: metastasen in 1 tot 3 regionale lymfeklieren.
- pN2: metastasen in 4 of meer regionale lymfeklieren.

Module 4 Communicatie en besluitvorming

Aanbeveling-1

Geef de patiënt mondelinge voorlichting. Mondelinge informatie door arts en verpleegkundig specialist is onvervangbaar.

Overweeg de terugvraagmethode te gebruiken om te controleren of de informatie goed is begrepen.

Aanbeveling-2

Ondersteun mondelinge voorlichting met:
- een betrouwbare website waar informatie over galweg- en galblaascarcinoom te verkrijgen is, zoals https://www.kanker.nl/kankersoorten/galwegkanker/algemeen/wat-is-galwegkanker
- informatie over het Patiëntenplatform Zeldzame Kankers (https://zeldzamekankers.nl/), die patiënten en naasten kan ondersteunen met advies, voorlichting, informatievoorziening en lotgenotencontact.

Aanbeveling-3

Informeer de patiënt over:
- het verwachte ziektebeloop en verwachte symptomatologie op basis van de diagnose, ziektebeloop in de afgelopen periode, co-morbiditeit en prognose;
- de voor- en nadelen van de verschillende behandelopties;
- welke centra meer expertise hebben op het gebied van dit tumortype voor een eventuele “second opinion” indien gewenst.

Bespreek met de patiënt aan welke informatie op welk moment behoefte is

Aanbeveling-4

Maak de patiënt duidelijk wie op welk moment in het zorgtraject de hoofdbehandelaar is.

Maak de patiënt duidelijk wie de casemanager is (verpleegkundig specialist of gespecialiseerde (oncologie) verpleegkundige).

Aanbeveling-5

Kom gezamenlijk met de patiënt tot een zorgplan door:
- patiënten van alle gewenste- en benodigde informatie te voorzien;
- patiënten uit te nodigen om deel te nemen aan de besluitvorming;
- de voorkeuren van patiënten vast te stellen;

- patiënten te ondersteunen in het maken van een beslissing.

Aanbeveling-6

Bied de patiënt de bijbehorende emotionele ondersteuning, daarbij kan ook:
- verwezen worden naar een psycholoog, pastoraal werker of maatschappelijk werker;
- informatie gegeven worden over de mogelijkheden voor lotgenotencontact.

Module 5 Nazorg en nacontrole

Aanbeveling-1 Vroege gevolgen van ziekte en behandeling: galwegobstructie

Informeer de patiënt en naasten over de mogelijke klachten en behandelingen van galwegobstructie door middel van geschreven informatie (obstructieklachten, koorts, pijn, gewichtsverlies).

Spreek in het oncologienetwerk duidelijk af op welke locatie welke nazorg plaatsvindt en bespreek dit concreet met de patiënt (eigen centrum dan wel centrum met meer expertise).

Aanbeveling-2 Vroege gevolgen van ziekte en behandeling

Signaleer regelmatig de vroege fysieke en psychosociale gevolgen van galblaas / galwegcarcinoom met behulp van (gevalideerde) signaleringsinstrumenten, startend vanaf diagnose.
- De richtlijn 'Detecteren behoefte psychosociale zorg' geeft meer informatie over meetmomenten, instrumenten en afkappunten.
- Wat betreft fysieke gevolgen kan gefocust worden op klachten van obstructie-icterus (jeuk, ontkleurde ontlasting en donkere urine) en cholangitis (koorts (>38,5°C) en koude rillingen). Hierbij kan gebruik gemaakt worden van het dagboek jeuk registratie (IKNL), de Lastmeter, Jeuk score (bijvoorbeeld VAS score), een score om de voedingstoestand te meten (bijvoorbeeld Must score), meten van pijnklachten (bijvoorbeeld VAS-pijnscore) en het Nazorgplan (zie bijlage).

Geef de patiënt een duidelijk aanspreekpunt bij fysieke / psychosociale klachten (voorkeur verpleegkundig specialist dan wel gespecialiseerde verpleegkundige).

Aanbeveling-3 Afstemmen van nazorg op de behoefte van de patiënt en informatie over late gevolgen

Bespreek de inhoud en organisatie van nazorg met de patiënt zodat dit kan worden aangepast aan de individuele behoefte.

Geef de patiënt en zijn huisarts goede voorlichting en instructie over mogelijke late gevolgen en hoe daarmee om te gaan (galwegobstructie klachten, koorts, jeuk, ascites, gewichtsverlies, vermoeidheid, passageklachten, pijn).

Informeer de patiënt bij welke zorgverlener hij bij het optreden van klachten terecht kan en neem dit op in het nazorgplan.

Zorg voor overdracht naar de huisarts.

Aanbeveling-4 Individueel nazorgplan

Maak voor elke patiënt een individueel nazorgplan dat is afgestemd op zijn restklachten en behoeften.

Zet het nazorgplan tenminste op de volgende momenten in:
- bij ontslag uit het ziekenhuis;
- bij de afronding van de primaire kankerbehandeling;
- indien er wijzigingen optreden in de medisch en/of psychosociale situatie van de patiënt of andere momenten van heroverweging van de nazorg.

Neem het nazorgplan van de patiënt op in elektronische databases en dossiers en te gebruiken voor interdisciplinaire overdracht, onder andere naar de huisarts.

Aanbeveling-5 detectie nieuwe kankermanifestaties

Informeer de patiënt over de mogelijkheden en beperkingen van vroege detectie van nieuwe manifestaties van kanker. Eerlijkheid over de beperkingen verdient de voorkeur omdat er geen bewijs is dat vroege opsporing zinvol is. Het voorkomt valse hoop en gaat onnodige medicalisering tegen.

Indien de patiënt na deze voorlichting aangeeft toch behoefte te hebben aan nacontrole dan kan dit individueel besproken en afgewogen worden.

Aanbeveling-6 organisatie nazorg

Organisatie nazorg
Maak afspraken over de taakverdelingen voor de nazorg, die aangeboden wordt in het ziekenhuis, de eerste- of derdelijns instellingen.

Zorg ervoor dat bij de afronding van primaire behandeling voor de nazorg een vaste contactpersoon voor iedere patiënt aangesteld wordt. Spreek dit multidisciplinair af in het team en met de huisarts.

Informeer de patiënt wie de vaste contactpersoon in de nazorg voor hem is. Leg dit vast in het nazorgplan voor de patiënt.

Zorg voor interdisciplinaire overdracht van informatie, zeker ook naar de huisarts, bijvoorbeeld via het nazorgplan van de patiënt.

Module 6 Cross-sectionele beeldvorming

Aanbeveling-1

Overweeg een MRI of echo met contrast voor patiënten met een galblaas afwijking als er op CT onvoldoende zekerheid is of er sprake is van een benigne of een (pre)maligne afwijking.

Aanbeveling-2

Overweeg een MRI voor de differentiatie met andere maligne leverlaesies (met name hepatocellulair carcinomen) bij patiënten met een verdenking op een intrahepatisch cholangiocarcinoom als dit het beleid kan wijzigen. Zie hiervoor ook de module diagnostiek in de richtlijn 'Hepatocellulair carcinoom'.

Aanbeveling-3

Overweeg een MRI als er op CT onzekerheid bestaat bij patiënten met een mogelijk resectabel perihiliair cholangiocarcinoom over de uitbreiding van de tumor in de galwegen (Bismuth-Corlette classificatie) en dit het beleid kan wijzigen.

Aanbeveling-4

Overweeg een MRI bij patiënten met intrahepatisch cholangiocarcinoom en galblaascarcinoom, die in aanmerking komen voor een resectie voor de detectie van occulte levermetastasen.

<u>Module 7 Locoregionale behandeling met TACE of SIRT voor iCCA</u>

Verricht geen standaard locoregionale therapie voor patiënten met lokaal-uitgebreid iCCA.

Overweeg locoregionale therapie (TACE of SIRT) voor patiënten met lokaal-uitgebreid iCCA als sprake is van een grote tumor dichtbij de leverhilus met dreigende galwegobstructie bij voorkeur in studieverband.

<u>Module 8 Preoperatieve vena porta embolisatie</u>

Verricht een percutane pre-operatieve vena portae embolisatie bij patiënten met galblaas of galwegkanker bij wie een leverresectie gepland wordt en het volume en/ of de functie van de future remant liver onvoldoende wordt geacht.

- Bij deze patiënten is het aannemelijk dat er onderliggend leverlijden is of galwegobstructie als etiologische factor. Daarom is het advies om een restvolume van minstens 40% aan te houden.

<u>Module 9 Indicatie resectie</u>

Aanbeveling-1

Verricht de beoordeling voor resectie van een galweg- of galblaascarcinoom in een centrum met chirurgische expertise van het galweg- en galblaascarcinoom.

Aanbeveling-2

Verricht geen resectie van het galweg- of galblaascarcinoom bij patiënten met metastasen (stadium IV). Hieronder vallen ook positieve extraregionale lymfklieren waaronder die bij de truncus coeliacus en in het aortocavale window.

Aanbeveling-3

Laat iedere patiënt met een galweg- of galblaascarcinoom in aanmerking komen voor resectie wanneer een complete (R0) resectie mogelijk lijkt.

Aanbeveling-4

Verricht een diagnostische laparoscopie voorafgaand aan een laparotomie bij alle patiënten met galweg- of galblaascarcinoom.

Aanbeveling-5

Verricht niet standaard een resectie bij patiënten met intrahepatisch cholangiocarcinoom en multifocale ziekte in de lever of positieve lymfklieren.

Aanbeveling-6

Verricht niet standaard een resectie bij patiënten met perihilair cholangiocarcinoom en meer dan 180 graden betrokkenheid van de arteria hepatica naar de toekomstige restlever of positieve lymfklieren.

Aanbeveling-7

Verricht niet standaard een resectie bij patiënten met galblaaskanker en een stille icterus bij presentatie of bij patiënten met positieve lymfklieren.

Aanbeveling-8

Voer geen cholecystectomie en follow-up uit bij patiënten met een galblaaspoliep ≤ 5 millimeter.

Verricht een één- tot maximaal twee-jarige echografische follow-up bij patiënten met een galblaaspoliep tussen 6-10 millimeter.

Verricht een cholecystectomie bij patiënten met een galblaaspoliep >10 millimeter, poliepen die meer dan 3 millimeter per jaar groeien en in patiënten met primaire scleroserende cholangitis (PSC).

Verricht geen cholecystectomie indien er een echografisch beeld is van adenomyomatosis, ook niet bij afwijkingen >1 centimeter.

Aanbeveling-9

Heroverweeg een resectie bij patiënten met een lokaal gevorderd galweg- of galblaascarcinoom en een goede response op systemische chemotherapie.

Module 10 Adjuvante systemische behandeling

Geef geen adjuvante behandeling na een in opzet curatieve resectie van een galweg- of galblaascarcinoom.

Module 11 Palliatieve systemische behandeling in de 1e lijn

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

Geef bij patiënten die in aanmerking komen voor palliatieve systemische therapie gemcitabine + cisplatin.

Geef ook gemcitabine + cisplatin bij geconjungeerde hyperbilirubine op basis van galwegobstructie; bij goede drainage is het niet nodig te wachten op normaliseren van het bilirubine.

Overweeg in geval van een contra-indicatie voor cisplatin, substitutie door oxaliplatin of geef gemcitabine monotherapie.

Module 12 Palliatieve systemische behandeling na de 1e lijn

Bepaal met behulp van Samen Beslissen of tweedelijns behandeling gestart dient te worden.

Bespreek de mogelijkheid van actieve symptoombestrijding indien er besloten wordt geen tumorgerichte tweedelijns behandeling te starten. Actieve symptoombestrijding zoals in de ABC-06 studie bestond uit elke 4 weken fysieke controle met leverwaarden en onder andere eventuele behandeling enzymsuppletie, maaguitgangstenose, galwegobstructie en cholangiosepsis.

Bespreek bij wens voor tweedelijns palliatieve systeemtherapie de behandeling met FOLFOX en bespreek ook dat deze winst gemiddeld beperkt is.

Overleg indien tweedelijns behandeling wordt overwogen met een centrum met voldoende expertise welke studies voorhanden zijn en welke aanvullende bepalingen (o.a. MSI, NTRK) verricht dienen te worden.

Het Kennisinstituut van de Federatie Medisch Specialisten
Toevoegen van richtlijn aan Richtlijnendatabase. Daarbij opnemen van dit implementatieplan op een voor alle partijen goed te vinden plaats.

Bijlage 1 Notulen 2e werkgroepvergadering richtlijnherziening Galweg- en galblaascarcinoom - bespreken resultaten schriftelijke knelpuntenanalyse

Datum: 3 november (16:30 – 18:30)
Locatie: Online (Zoom)

Aanwezig: Bas Groot Koerkamp (NVvH), Joris Erdman (NVvH), Philip de Reuver (NVvH), Heinz-Jozef Klumpen (NIV), Lydi van Driel (NVMDL), Chulja Pek (V&VN), Marieke de Boer (NVvH), Nadia Haj Mohammad (NIV), Otto van Delden (NVvR), Marga Schrieks (NFK), Anke Bode (NFK), Michiel Oerbekke (Kennisinstituut), Linda Oostendorp (Kennisinstituut)

Afgemeld: Francois Willemsen (NVvR), Joanne Verheij (NVVP), Dagmar Nieboer (Kennisinstituut),

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Actie -en besluitenlijst

Acties
Actie Kennisinstituut: opschonen raamwerk en werkgroepleden uitnodigen zich in te schrijven voor modules.
Actie werkgroepleden: inschrijven voor modules en vervolgens in subgroepjes werken aan het vaststellen van uitgangsvragen en het maken van PICO's met ondersteuning van het Kennisinstituut
Actie Marga en Anke: verdiepen in de module 'Communicatie en besluitvorming' die al ontwikkeld is voor de richtlijn Colorectaal carcinoom.
Actie Kennisinstituut: uitsturen datumprikker voor derde werkgroepvergadering in de tweede of derde week van januari 2021

Besluiten
De 13 eerder geformuleerde knelpunten zullen allemaal uitgewerkt worden. De toegevoegde knelpunten vallen allemaal onder al bestaande knelpunten.
Er zal een module 'Communicatie en besluitvorming' worden toegevoegd, naar voorbeeld van een zelfde module voor de richtlijn Colorectaal carcinoom.
In de nieuwe richtlijn zullen binnen ieder hoofdstuk (diagnostiek, behandeling, etc) subkopjes gemaakt worden per tumortype

1. Kennismaking nieuwe werkgroepleden + belangen bespreken

De nieuwe werkgroepleden Nadia, Marieke, Otto en Anke stellen zich voor. Er worden geen belangen gemeld. Vanuit het Kennisinstituut stellen Linda en Michiel zich voor, zij zullen de taken van Dagmar tijdens haar zwangerschapsverlof overnemen.

2. Raamwerk: input invitational bespreken + vaststellen knelpunten

Er is budget beschikbaar voor 13 modules. Normaal gesproken wordt er voor iedere module een literatuurzoektocht uitgevoerd, maar omdat het hier om een zeldzame kanker gaat en de hoeveelheid literatuur beperkt is, is er één brede search uitgevoerd om alle literatuur over galweg- en galblaascarcinomen te identificeren. Dit zal verdeeld worden in pakketjes per uitgangsvraag.

Voor het hoofdstuk Diagnostiek waren drie knelpunten geformuleerd en zijn vijf nieuwe punten aangedragen. De vijf nieuwe punten overlappen, punt 1 en 5 betreffen diagnostiek bij patiënten met een indeterminate galwegstrictuur en punt 2, 3 en 4 betreffen moleculaire diagnostiek. Deze punten zijn specificaties van de al eerder geformuleerde drie knelpunten en kunnen meegenomen worden bij het formuleren van de uitgangsvragen. Er hoeven dus geen knelpunten toegevoegd te worden.

Voor het hoofdstuk Chirurgische behandeling waren vier knelpunten geformuleerd en zijn vier nieuwe punten aangedragen. Twee van deze nieuwe punten betreffen levertransplantatie, hiervoor kan verwezen worden naar informatie van het Landelijk Overleg Levertransplantatie (LOL). Voor de huidige richtlijn is het van belang om te definiëren welke patiënten niet in aanmerking komen voor resectie en doorverwezen dienen te worden voor levertransplantatie. De criteria voor resectie komen aan de orde in knelpunt 3. Het aangedragen punt over stents valt onder drainage (knelpunt 5). De resectiecriteria voor een galblaaspoliep vallen onder knelpunt 4.

Drainage is niet per definitie een chirurgische behandeling, in de vergadering werd voorgesteld een hoofdstuk ’overige behandeling’ toe te voegen waarin drainage (zowel pre-operatief als palliatief) en vena porta embolisatie zullen worden behandeld. Daarmee zouden behandelingen worden verdeeld in ’chirurgisch’, ’systemisch’ en ’overig’. Na afloop van de vergadering is in overleg tussen het Kennisinstituut en Bas besloten dat het logischer is om porta embolisatie te vatten onder chirurgisch, gezien dit een voorbereidende interventie is voor operatie. Locoregionale behandeling valt dan samen met galweg drainage onder overige behandeling.

Het hoofdstuk Radiotherapeutische behandeling zal worden vervangen door het hoofdstuk ’Overige behandeling’ zoals hierboven beschreven.

Voor het hoofstuk Systemische behandeling zal de indeling van de behandelingen worden aangepast in (neo)adjuvant (knelpunt 9) en inductie/palliatief (knelpunt 10). Onder locoregionale behandeling vallen onder andere radiotherapie, nanoknife, pump, SIRT etc. Deze vallen onder het nieuwe hoofdstuk ’Overige behandeling’. Drie van de vier nieuwe punten hebben betrekking op adjuvante en inductie behandeling, en het punt met betrekking tot mutatie gerichte behandeling komt aan de orde zowel in het hoofdstuk diagnostiek als systemische behandeling.

Voor het hoofdstuk Pathologie was één knelpunt geformuleerd. Er is een nieuw punt aangedragen met betrekking tot het verkrijgen van PA. De criteria voor het verrichten van een biopt komen aan de orde in knelpunt 2 in het hoofdstuk Diagnostiek. Een subvraag hierbij kan zijn hoe dit biopt verricht dient te worden.

Voor het hoofdstuk Nazorg en follow-up was één knelpunt geformuleerd. Hierbij wordt opgemerkt dat nazorg niet alleen van toepassing is na chirurgische resectie, maar ook in de palliatieve fase.
Er zijn ook drie nieuwe punten aangedragen. Er zal een nieuwe module 'Communicatie en besluitvorming' aan de richtlijn worden toegevoegd. Voor de richtlijn 'Colorectaal carcinoom' is al een dergelijke module ontwikkeld, deze kan als uitgangspunt worden gebruikt. Het onderwerp 'casemanagement' is relevant voor meerdere tumorsoorten, mogelijk is hier eerder al informatie voor ontwikkeld die we als uitgangspunt kunnen gebruiken. Het derde aangedragen punt (ontbreken van een protocol) zal worden meegenomen in knelpunt 13.

Het patiëntenperspectief wordt toegelicht door Marga. Veel van de aangedragen punten passen binnen de module 'Communicatie en besluitvorming'. Patiënten waarderen het als de informatie overzichtelijk wordt gepresenteerd, bijvoorbeeld in de vorm van een beslisboom. Na het uitwerken van de vragen kan bekeken worden of het inderdaad mogelijk is om een beslisboom te onwikkelen.
Logistieke aspecten zijn bij deze zeldzame kanker extra relevant, vanwege de verwijzing vanuit de regio naar een expertcentrum. Op het gebied van Nazorg blijkt er veel onduidelijkheid te zijn.

Algemene punten

Om zo efficient mogelijk te werken zal goed gekeken worden welke informatie al beschikbaar is. We willen zoveel mogelijk aansluiten bij bestaande documenten om dubbel werk en tegenstrijdigheden te voorkomen. Zo kunnen we bijvoorbeeld verwijzen naar de SONCOS normen en informatie van de NVvH en het Landelijk Overleg Levertransplantatie (LOL).

Als over bepaalde onderwerpen geen wetenschappelijke informatie beschikbaar is kan dit worden opgenomen in het overzicht van kennislacunes. Vanuit de patiëntenvereniging wordt ook gewerkt aan een lijst met onderzoeksprioriteiten.

In deze richtlijn worden vier (vijf indien poliepen ook aan bod komen) ziektebeelden opgenomen met ieder een eigen TNM stadiëring. Voor systemische behandeling worden alle tumoren vaak samen genomen. Diagnostiek zal verschillend zijn voor ieder tumor type en ook voor chirurgie en drainage zal naar verwachting in de literatuur onderscheid gemaakt worden tussen de verschillende tumor types. De gebruikers van de richtlijn zijn voornamelijk de verwijzers naar de expertcentra. Er zal een inleidende tekst geschreven worden over de verschillende tumortypes. Om te zorgen dat de informatie makkelijk te vinden is en om toekomstig modulair onderhoud makkelijker te maken zullen voor ieder hoofdstuk subkopjes gemaakt worden per tumortype.

3. Vervolgafspraken

Michiel en Linda zullen het raamwerk opschonen en beschikbaar maken op Viadesk zodat alle werkgroepleden hun voorkeur kunnen aangeven. Per knelpunt zijn minimaal twee werkgroepleden nodig, waarvan één de trekker zal zijn. In subgroepjes zal dan vervolgens gewerkt worden aan het vaststellen van uitgangsvragen en het maken van PICO's. Dit zal vervolgens besproken worden in de volgende werkgroepvergadering. Er zal een datumprikker gestuurd worden voor een vergadering in de tweede of derde week van januari 2021.

Veel van de door patiënten aangedragen punten vallen onder de module ’Communicatie en besluitvorming’. Marga en Anke zullen zich verdiepen in de vergelijkbare module die al ontwikkeld is voor de richtlijn Colorectaal carcinoom.

4. Rondvraag en sluiting

Marieke zal naar verwachting niet beschikbaar zijn van april tot en met juni 2021.