HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Chemosaturation with percutaneous hepatic perfusion for patients with liver cancer

Systematic Review

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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List of abbreviations

AFP .....alpha-fetoprotein
AJCC .....American Joint Committee on Cancer
AMSTAR .....A MeaSurement Tool to Assess systematic Reviews
AWMF .....Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (Association of the Scientific Medical Societies)
CRADA.....Cooperative Research and Development Agreement
CRD .....Centre for Reviews and Dissemination
CTCAE .....Common Terminology Criteria for Adverse Events
DARE.....Database of Abstracts of Reviews of Effects
DKG.....Deutschen Krebsgesellschaft e.V.

DKH.....Deutschen Krebshilfe
DRG.....Diagnosis Related Groups
EUdraCT.....European Union Drug Regulating Authorities Clinical Trials Database
EUnetHTA.....European network for Health Technology Assessment
FDA.....Food and Drug Administration
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
HAI.....hepatic artery infusion
HCC.....hepatocellular carcinoma
HTA.....Health Technology Assessment
ICD-10.....International Classification of Diseases, Tenth Revision
IE.....immunoembolisation
IHE.....Institute of Health Economics
IHP.....isolated hepatic perfusion
INV.....investigator assessment
IRC.....image review committee
LITT.....laser-induced interstitial thermotherapy
LUMPO.....Liverpool Uveal Melanoma Prognosticator Online
M-PHP.....Melphalan percutaneous hepatic perfusion
n.....number of patients/studies
NA.....not available
NAFLD.....non-alcoholic fatty liver disease
NASH.....non-alcoholic fatty liver hepatitis
NHS-EED.....National Health Service – Economic Evaluation Database
NICE.....National Institute for Health and Care Excellence
NL.....The Netherlands
NR.....not reported
PHP.....percutaneous hepatic perfusion
PRISMA.....Preferred Reporting Items for Systematic Reviews and Meta-Analyses
pts.....patients
RCT.....randomised controlled trial
RFA.....radio frequent ablation
RoB.....risk of bias
s.s.....statistisch signifikant
SIRT.....selective internal radiotherapy
TACE.....transarterial chemoembolisation
TNM.....Tumour-Node-Metastasis
UK.....United Kingdom
USA.....United States of America
WHO.....World Health Organisation
yrs.....years

Executive summary

Introduction

Health Problem

primärer Leberkrebs mit schlechter Prognose

Hepatocellular carcinoma is the most frequent form of *primary* liver cancer, with mortality rates almost the same as incidences rates. This disease is relatively rare, but it is one of the ten most frequent causes of cancer deaths in Austria due to its poor prognosis. In 2019, in Austria, a total number of new liver cancer patients of 1,025 was recorded with 867 deaths. The most common risk factors are liver cirrhosis, chronic hepatitis B and C virus infection and alcohol consumption, followed by diabetes and adiposity.

sekundärer Leberkrebs ist häufiger

Metastases to the liver (*secondary* liver cancer) are more common than primary liver tumours. Even if the primary tumour is successfully treated, up to 50% of patients eventually develop metastatic diseases with predominant liver involvement. In patients with only one site of metastasis, the liver is involved in 95% of cases.

Lebermetastasen durch Augen-, Aderhaut- und Hautmelanome

Melphalan percutaneous hepatic perfusion (M-PHP), a non-surgical treatment alternative, is performed in patients with primary or secondary liver cancer. In Europe, in 2016, most M-PHP procedures were performed and investigated in patients with hepatic metastases from ocular melanoma. Hepatic metastases from ocular, uveal, and cutaneous melanoma are the diseases in the scope of this assessment.

Leber in 89 % predominant (Augenmelanom)

Ocular melanoma is, after cutaneous melanoma, the second most common type of hepatic metastases. The liver is the most common sole site of metastatic diseases (up to 50%) after primary cancer treatment. In 89% of patients with ocular melanoma developing metastases, the liver is the predominant metastatic site. In comparison, only 10-20% of patients with metastases from cutaneous melanoma develop liver and bowel metastases.

schlechte Prognose aufgrund eingeschränkter Therapiemöglichkeiten

geographische Unterschiede

Hepatic metastases from melanoma are a crucial determinant of the survival and clinical course of the affected patients. The median survival rate is estimated to be less than nine months in patients with metastatic ocular melanoma. Once liver metastases occur, it carries a very poor prognosis as no established, effective alternative or systemic locoregional treatments exist. The incidence varies with the geographical latitude for hepatic metastases from uveal melanomas. It is higher in North than South Europe due to a positive association with light eye colour, fair skin, and Caucasian ethnicity.

intra-arterielle und hyperthermische Therapien

The current clinical management of unresectable primary and secondary liver cancer can be divided into intra-arterial and hyperthermic therapies. Intra-arterial therapies include, e.g., hepatic artery infusion, transarterial chemoembolisation, selective internal radiotherapy and immunoembolisation. Hyperthermic therapies include, e.g., radio frequent ablation and laser-induced interstitial thermotherapy.

Chemo- und regionale Therapie bei sekundärem Leberkrebs

In patients with *metastatic* disease, chemotherapy improves survival and quality of life. However, systemic therapy is limited in number and efficacy for patients with metastatic ocular melanoma, often presenting unresectable liver metastases. Regional therapies deliver dose-intensive treatment to the liver while limiting unnecessary systemic toxicities. They include hepatic arterial infusions, chemoembolisation, isolated hepatic perfusions, and PHP. The

clinical practice guideline of the German Association of the Scientific Medical Societies mentioned PHP as a local therapeutic procedure, but there is no recommendation for use given yet.

Description of Technology

Hepatic CHEMOSAT® Delivery System

The medical device Hepatic CHEMOSAT® Delivery System is used to treat patients with surgically unresectable primary or secondary liver tumours. This system has been developed as an alternative non-operative treatment from Delcath Systems Inc., New York.

perkutane Leberperfusion: wiederholbar und minimal-invasiv

Chemosaturation with PHP represents a repeatable and minimally invasive alternative to isolated hepatic perfusion requiring only percutaneous access. The liver is isolated from the systemic circulation and directly and subsequently perfused with a high dose of the chemotherapeutic agent melphalan.

limitierte chemotherapeutische Belastung

Therefore, systemic exposures are limited. However, some leak of the therapeutic agent into the systemic circulation occurs because the vascular isolation of the liver is not achieved completely. To reduce high rates of hematologic toxicity, a new hemofiltration system with a second-generation detoxification cartridge was developed. Recently, M-PHP has been adopted as a first-line treatment for patients with metastatic ocular melanoma in the Netherlands.

Methods

NICE Leitlinie

We could identify a systematic review from NICE with the same research question via hand search, which we critically appraised in AMSTAR 2, resulting in low overall confidence. This review was used to identify relevant studies. In addition, a systematic literature search for (non-)randomised controlled trials, and prospective case series was conducted for the time period not covered by the selected review.

systematische Literatursuchen

The systematic update literature search (12/2020 to 12/2021) was conducted in four databases. Overall, 160 hits were identified. We further identified 11 studies from the NICE guidance, one study through a second systematic search (focusing on systematic reviews), and two from the manufacturer. Two independent researchers screened the references, and in case of disagreement, a third researcher was involved in solving the differences.

Datenanalyse und -synthese

The data from the selected studies were systematically extracted into data extraction tables. The single-data extraction method with verification by another researcher was used. Studies were systematically assessed for internal validity and risk of bias by two independent researchers. Data on each selected (critical) outcome category were, if applicable, synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation).

Domain effectiveness

entscheidungsrelevante Endpunkte:

In discussion with clinical experts, the following effectiveness outcomes were defined as most relevant and *crucial* to derive a recommendation: overall survival, overall and hepatic progression-free survival, and quality of life.

Effektivität und …

Domain safety

… Sicherheit

Death was defined as most relevant to patients and, therefore, crucial to derive a recommendation.

Results

Available evidence

No studies regarding primary liver cancer could be identified.

1 RCT

For secondary liver cancer, the evidence included in the effectiveness domain consists of one multicentre phase III randomised controlled trial (RCT). Patients of the control group crossed over to the treatment arm if they had evidence of disease progression. The first generation of the CHEMOSAT® Delcath Systems was compared to the best alternative care, mainly systemic chemotherapy and chemoembolisation.

Filter erster Generation

sekundärer Leberkrebs von Augen- und Hautmelanom

Patients (n=93; median age 55.5) with unresectable ocular or cutaneous melanoma metastatic to the liver were recruited in the RCT. Considering only the patients receiving the intervention (M-PHP), a total of 70 patients were observed, i.e., patients randomised to the M-PHP group (n=42) *and* after crossover to M-PHP group (n=28).

1 Fallserie

In the safety domain, the evidence consists of one further observational study. Patients (n=35; median age 59 years) with unresectable ocular melanoma metastases confined to the liver were recruited. The second generation of the CHEMOSAT® Delcath Systems was used.

Filter zweiter Generation

Verzerrungsrisiko und Qualität der Evidenz

The overall risk of bias was moderate (observational study) to high (RCT). Overall strength of evidence for the *efficacy* of PHP compared to best alternative care was low to moderate and for *safety* very low in all outcomes.

Clinical effectiveness

Lebensqualität: keine Evidenz

There is no available evidence regarding primary liver cancer and the outcome quality of life.

Gesamtüberleben: nicht statistisch signifikant (s.s.)

In the identified RCT, the median *overall survival* was 10.6 months (95% CI 6.9-13.6 months) in the M-PHP group compared with 10.0 months (95% CI 6.0-13.1 months) in the control group receiving best alternative care, with no statistically significant difference between the two groups ($p>0.05$).

allgemein-progressionsfreies Überleben: s.s.

The median *overall progression-free survival* in the M-PHP group was statistically significantly longer (5.4 months [95% CI 3.4-8.1 months]) than in the control group (1.6 months [95% CI 1.5-2.3 months]) with a p-value of $p<0.0001$.

hepatisch-progressionsfreies Überleben: s.s.

Median *hepatic progression-free survival* was statistically significantly longer ($p<0.0001$) in the M-PHP group (7.0 months [95% CI 5.2-9.7 months]) compared to the control group (1.6 months [95% CI 1.5-2.9 months]).

(hepatisch-)objektive Ansprechrate: s.s.

A statistically significant improvement favouring the M-PHP group could be found when comparing *hepatic objective response* between the two groups ($p<0.001$). The *objective response rate* was statistically significantly higher in the M-PHP group compared to the control group, with a p-value of $p<0.01$.

Safety

No evidence regarding primary liver cancer could be identified.

4 Todesfälle (RCT), keine Todesfälle (Fallserie)

In the RCT, 4.3% (n=4/93 patients) adverse events that caused *death* were reported, whereof three deaths were attributed to M-PHP (1 study). No deaths were reported in the observational study (1 study).

~90 % peri- und post-prozessuale Ereignisse (Grad 3) (RCT)

Peri-procedural events (grade 3/4 events) were observed in 90% of all M-PHP treated patients group (n=63/70 patients) in the RCT. *Post-procedural events* (grade 3/4 events) were observed in 91.4% (n=64/70 patients) (1 study).

unerwünschte und (nicht-)hämatologische/-hepatische Ereignisse (Fallserie)

In the observational study, *serious adverse events* occurred in 14 (2%) of 67 procedures. Regarding *non-hematologic and non-hepatic complications*, all-grades events occurred in 58 (87%), grade 3 events in 14 (21%), and grade 4 events in one (2%) of 67 procedures. *Hematologic grade 4 late events* occurred, such as thrombocytopenia (11/62 procedures [17.7%]), leukopenia (22/62 procedures [35.5%]), and neutropenia (26/62 procedures [42.6%]). *Hepatic all-grade late events* occurred, such as increased alanine aminotransferase (36/62 procedures [58.1%]), increased aspartate aminotransferase (21/60 procedures [35.0%]), and increased bilirubin (6/60 procedures [10.0%]), but no grade 3 or 4 events (1 study).

17 % Herztoxizität (RCT)

In the RCT, *peri-procedural events* such as cardiac toxicity were reported in 12 patients (17.1%). *Post-procedural events* were related to the effects of bone marrow suppression (1 study).

s.s. Aminotransferasen-Anstieg (Fallserie)

In the observational study, there were no grade 3 and 4 *hepatic events*, a statistically significant increase ($p<0.01$) of aminotransferases was observed, indicating some degree of hepatic toxicity (1 study).

Behandlungsabbrüche: 96 % (RCT) und 8 % (Fallserie)

In the RCT, 67 (95.8%) of 70 patients treated with M-PHP *therapy discontinued*, mainly due to adverse events and disease progression (1 study). In the observational study, in five (7.5%) of 67 procedures, discontinuation of therapy was described mainly due to filter clotting (1 study).

Upcoming evidence

1 laufende RCT

The search for ongoing studies revealed that there is currently one ongoing RCT in the USA sponsored by Delcath Systems Inc. This trial compares efficacy, safety and pharmacokinetics of M-PHP given sequentially following cisplatin/gemcitabine versus cisplatin/gemcitabine (standard of care) in patients with intrahepatic cholangiocarcinoma (n=295). The estimated completion date is May 2023.

Reimbursement

derzeit keine Kostenrückerstattung von M-PHP in Österreich

The Hepatic CHEMOSAT® Delivery System has been approved in Europe since 2012 and holds a CE marking. In the USA, approval of the Food and Drug Administration is being prepared. In Austria, M-PHP is currently not included in the catalogue of benefits (LKF, leistungsorientierte Krankenanstaltenfinanzierung) and, hence, it is not a fully reimbursable service. Germany is the only European country with reimbursement by health insurance.

Discussion

Effektivität teilweise gegeben

Evidence was found indicating that M-PHP compared to best available care may be more effective regarding overall and hepatic progression-free survival. No evidence concerning quality of life could be found, and overall survival did not statistically significantly improve due to M-PHP compared to best available care.

Gesamtüberleben: nicht s.s. ev. aufgrund hoher Crossover-Rate

The failure demonstrating a benefit of M-PHP on *overall survival* in the RCT may be due to the high cross over of the control group, which may have confounded any possible overall survival advantage. Furthermore, a substantial number of patients had extrahepatic metastases, which might limit the liver-directed therapy's optimal effect.

Three of four *deaths* were attributed to M-PHP. *Procedure-related complications* were observed in the majority of patients, and many *discontinued* M-PHP therapy. The small number of included participants across the studies could have influenced the occurrence of safety events. However, this can be explained by the rarity of the disease. Furthermore, filters of generations 1 and 2 were used in the included studies, which also may affect the generalisability derived from safety results.

4 Todesfälle

Komplikationen und Behandlungsabbrüche

The committee of the NICE guidance stated that the procedure's toxicity is principally related to how efficiently melphalan is removed and prevented from entering the patient's systemic circulation. Furthermore, systemic toxicity may be attributed to other factors and not only to incomplete filtration. However, our results support the reasoning of NICE, stating that the evidence of safety shows serious, well-recognised complications.

NICE: Toxizität und schwerwiegende Komplikationen

Conclusion

The given evidence is insufficient and with limited internal and external validity to show clinical benefits of M-PHP in patients with secondary liver cancer compared to best available care. The only RCT demonstrated that M-PHP is more effective in overall and hepatic progression-free survival than best available care. Overall survival did not statistically significantly improve due to M-PHP. However, serious, well-recognised complications regarding safety outcomes were shown.

Effektivität teilweise gegeben, jedoch schwerwiegende Komplikationen

Due to the overall very low strength of evidence and high RoB of the RCT, no definitive conclusions on the effectiveness of M-PHP compared to best available care can be drawn. Further results from well-designed RCTs are lacking, and results of ongoing studies are to be awaited.

Evidenz unzureichend

Therefore, the evidence indicates that the inclusion of PHP for secondary liver cancer in the catalogue of benefits can not be supported at this time. New study results will potentially influence the effect estimate considerably. A large RCT (>200 patients) with patient-relevant primary outcomes is ongoing (NCT03086993). Therefore, a re-evaluation is recommended in 2024.

Neubewertung 2024

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

hepatocellular carcinoma: most frequent form of primary liver cancer with dismal prognosis

Leberzellenkrebs (Hepatozelluläres Karzinom) ist die häufigste Form des primären Leberkrebses, wobei die Sterblichkeitsrate fast der Inzidenzrate entspricht. Diese Erkrankung ist zwar relativ selten, gehört jedoch aufgrund der schlechten Prognose zu den zehn häufigsten Krebstodesursachen in Österreich. Im Jahr 2019 wurden in Österreich insgesamt 1.025 Neuerkrankungen an Leberkrebs und 867 Todesfälle verzeichnet. Die häufigsten Risikofaktoren sind Leberzirrhose, chronische Hepatitis-B- und -C-Virusinfektion und Alkoholkonsum, gefolgt von Diabetes und Adipositas.

secondary liver cancer more common

Metastasen in der Leber (sekundärer Leberkrebs) sind häufiger als primärer Leberkrebs. Selbst wenn der Primärtumor erfolgreich behandelt wird, entwickeln bis zu 50 % der Patient*innen Metastasen, prädominant in der Leber. Bei Patient*innen mit nur einem Metastasenherd ist die Leber in 95 % der Fälle betroffen.

hepatic metastases from ocular, uveal, and cutaneous melanoma

Die perkutane Leberperfusion mit Melphalan (M-PHP), eine nichtoperative Behandlungsalternative, wird bei Patient*innen mit primärem oder sekundärem Leberkrebs durchgeführt. In Europa wurden 2016 die meisten M-PHP-Verfahren bei Patient*innen mit Lebermetastasen eines Augenmelanoms durchgeführt und untersucht. Lebermetastasen durch Augen-, Aderhaut- und Hautmelanome sind die Indikationen, die in den Fokus dieser Übersichtsarbeit fallen.

liver predominant in 89% (ocular melanoma)

Das Augenmelanom ist, nach dem Hautmelanom, die zweithäufigste Art von Lebermetastasen. Die Leber ist der häufigste alleinige Ort für metastatische Erkrankungen (bis zu 50 %) nach einer primären Krebsbehandlung. Bei 89 % der Patient*innen mit Augenmelanom, die Metastasen entwickeln, ist die Leber die vorherrschende Metastasierungsstelle. Im Vergleich dazu entwickeln nur 10-20 % der Patient*innen mit Metastasen durch Hautmelanom Leber- und Darmmetastasen.

poor prognosis due to limited treatment options

Lebermetastasen eines Melanoms sind ein entscheidender Faktor für das Überleben und den klinischen Verlauf der betroffenen Patient*innen. Die mediane Überlebensrate bei Patient*innen mit metastasiertem Augenmelanom wird auf weniger als neun Monate geschätzt. Sobald Lebermetastasen auftreten, ist die Prognose sehr schlecht, da es keine etablierten, wirksamen Alternativen oder systemischen lokoregionalen Behandlungen gibt. Die Inzidenz von Lebermetastasen durch Aderhautmelanomen variiert je nach geografischem Breitengrad. Sie ist in Nordeuropa höher als in Südeuropa, was auf eine positive Assoziation mit heller Augenfarbe, heller Haut und kaukasischer Ethnizität zurückzuführen ist.

geographical differences

intra-arterial and hyperthermic therapies

Die derzeitige klinische Behandlung von inoperablem primärem und sekundärem Leberkrebs kann in intra-arterielle und hyperthermische Therapien unterteilt werden. Zu den intra-arteriellen Therapien gehören z. B. Infusion in die Leberarterie, transarterielle Chemoembolisation, selektive interne Strahlentherapie und Immunoembolisation. Zu den hyperthermischen Therapien gehören z. B. Radiofrequenzablation und laserinduzierte interstitielle Thermotherapie.

chemo and regional therapy for secondary liver cancer

Bei Patient*innen mit *metastasierter* Erkrankung verbessert eine Chemotherapie das Überleben und die Lebensqualität. Bei Patient*innen mit metastasiertem Augenmelanom, die häufig nicht inoperable Lebermetastasen aufweisen, ist die Chemotherapie jedoch in ihrer Anzahl und Wirksamkeit begrenzt. Regionale Therapien ermöglichen eine dosisintensive Behandlung der Leber und begrenzen gleichzeitig unnötige systemische Toxizität. Dazu gehören arterielle Leberinfusionen, Chemoembolisation, isolierte Leberperfusionen und perkutane Leberperfusion (PHP). In der klinischen Praxisleitlinie der deutschen Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften wird die PHP als lokales Therapieverfahren erwähnt, aber es gibt noch keine Empfehlung für eine Verwendung.

guideline: no recommendation for PHP

Beschreibung der Technologie

Hepatic CHEMOSAT® Delivery System

Das Produkt Hepatic CHEMOSAT® Delivery System wird zur Behandlung von Patient*innen mit chirurgisch inoperablen primären oder sekundären Lebertumoren eingesetzt. Dieses System wurde von Delcath Systems Inc. in New York als mögliche nicht-operative Behandlung entwickelt.

percutaneous liver perfusion: repeatable and minimally invasive

Die Chemosaturation mit PHP stellt eine wiederholbare und minimalinvasive Alternative zur isolierten hepatischen Perfusion dar, die nur einen perkutanen Zugang erfordert. Die Leber wird vom systemischen Kreislauf isoliert und anschließend direkt mit einer hohen Dosis des Chemotherapeutikums Melphalan durchströmt. Aufgrund der Isolation ist die systemische Belastung begrenzt. Da die vaskuläre Isolierung der Leber jedoch nicht vollständig erreicht wird, gelangt das Therapeutikum teilweise in den systemischen Kreislauf. Um hämatologische Toxizität zu verringern, wurde ein neues Hämofiltrationssystem zweiter Generation entwickelt. Kürzlich wurde M-PHP in den Niederlanden als Erstlinienbehandlung für Patient*innen mit metastasiertem Augenmelanom eingeführt.

limited systemic exposure

Methoden

NICE guidance

Per Handsuche konnten wir eine systematische Übersichtsarbeit des Nationalen Instituts für Gesundheit und Qualität (NICE) mit derselben Forschungsfrage identifizieren, welche in AMSTAR 2 durchgeführt wurde, was zu einer geringen Qualität der Übersichtsarbeit führte. Diese Übersichtsarbeit wurde zur Identifikation relevanter Studien herangezogen. Zusätzlich wurde für den Zeitraum, welcher nicht von der ausgewählten Übersichtsarbeit abgedeckt wurde, eine systematische Literatursuche nach (nicht-)randomisierten kontrollierten Studien und prospektiven Fallserien durchgeführt.

systematic literature searches

Die systematische Update-Literatursuche (12/2020 bis 12/2021) wurde in vier Datenbanken durchgeführt. Insgesamt wurden 160 Treffer ermittelt. Darüber hinaus identifizierten wir elf Studien aus der NICE-Leitlinie, eine Studie durch eine zweite systematische Suche (mit Schwerpunkt auf systematischen Übersichtsarbeiten) und zwei Studien des Herstellers. Zwei unabhängige Wissenschafterinnen überprüften die Referenzen, und im Falle von Unstimmigkeiten wurde ein dritter Wissenschafter zur Klärung der Differenzen hinzugezogen.

data analysis and synthesis

Die Daten aus den ausgewählten Studien wurden von einer Wissenschafterin systematisch in Datenextraktionstabellen extrahiert und von einer zweiten Wissenschafterin kontrolliert. Weiters wurden die Studien von zwei unabhängigen Forscherinnen systematisch auf ihre interne Validität und das Verzerrungsrisiko geprüft. Die Daten zu den (entscheidungsrelevanten) End-

punkten wurden gemäß GRADE (Grading of Recommendations Assessment, Development and Evaluation) studienübergreifend synthetisiert. Angesichts der Art der verfügbaren Daten beschränkte sich die Berichterstattung über die Ergebnisse auf einen narrativen Überblick; statistische Analysen wurden nicht durchgeführt.

Klinische Wirksamkeit

crucial effectiveness outcomes

In Diskussion mit klinischen Expert*innen wurden die folgenden Wirksamkeits-Endpunkte als besonders patientenrelevant und entscheidend für die Ableitung einer Empfehlung definiert: Gesamtüberleben, allgemein-progressionsfreies Überleben, hepatisch-progressionsfreies Überleben und Lebensqualität.

Sicherheit

crucial safety outcome

Todesfälle wurde als für die Patient*innen entscheidungsrelevant für die Ableitung einer Empfehlung definiert.

Ergebnisse

Verfügbare Evidenz

Es konnten keine Studien zu primären Leberkrebs identifiziert werden.

1 RCT

first-generation filter

Bei sekundärem Leberkrebs besteht die Evidenz hinsichtlich der Wirksamkeits-Endpunkte aus einer multizentrischen randomisierten kontrollierten Phase-III-Studie (RCT). In dieser gingen Patient*innen aus der Kontrollgruppe in die Behandlungsgruppe über (Crossover), wenn sie Anzeichen für ein Krankheitsfortschreiten aufwiesen. Die erste Generation des CHEMOSAT® Delcath Systems wurde mit der besten alternativen Behandlung, hauptsächlich systemische Chemotherapie und Chemoembolisation, verglichen.

secondary liver cancer from ocular or cutaneous melanoma

Es wurden Patient*innen (n=93; Median 55,5 Jahre) mit inoperablen Lebermetastasen durch Augen- oder Hautmelanome in der RCT rekrutiert. Unter Berücksichtigung der Patient*innen, welche die Intervention (M-PHP) erhielten, wurden insgesamt 70 Patient*innen beobachtet, d. h. Patient*innen, die in die M-PHP-Gruppe randomisiert wurden (n=42) und nach Crossover in die M-PHP-Gruppe (n=28).

1 case series

second-generation filter

Hinsichtlich der Sicherheit von M-PHP besteht die Evidenz aus einer weiteren Beobachtungsstudie. Patient*innen (n=35; Median 59 Jahre) mit inoperablen Lebermetastasen durch Augenmelanome wurden rekrutiert. Es wurde die zweite Generation des CHEMOSAT® Delcath Systems verwendet.

risk of bias and quality of evidence

Das Gesamtverzerrungsrisiko war moderat (Beobachtungsstudie) bis hoch (RCT). Die Gesamtstärke der Evidenz für die Wirksamkeit von PHP im Vergleich zur besten alternativen Behandlung war gering bis mäßig und für die Sicherheit sehr gering in allen Endpunkten.

Klinische Wirksamkeit

quality of life

Es liegt keine Evidenz zu primären Leberkrebs und Lebensqualität vor.

overall survival: not statistically significant (s.s.)

In der identifizierten RCT betrug das mediane *Gesamtüberleben* 10,6 Monate (95 % CI 6,9-13,6 Monate) in der M-PHP-Gruppe im Vergleich zu 10,0 Monaten (95 % CI 6,0-13,1 Monate) in der Kontrollgruppe, welche beste alternative Behandlung erhielt, wobei kein statistisch signifikanter Unterschied zwischen den beiden Gruppen bestand (p>0,05).

Das mediane *progressionsfreie Gesamtüberleben* war in der M-PHP-Gruppe statistisch signifikant länger (5,4 Monate [95 % CI 3,4-8,1 Monate]) als in der Kontrollgruppe (1,6 Monate [95 % CI 1,5-2,3 Monate]), mit einem p-Wert von p<0,0001.

overall progression-free survival: s.s.

Das mediane *hepatisch-progressionsfreies Überleben* war in der M-PHP-Gruppe statistisch signifikant länger (p<0,0001) als in der Kontrollgruppe (1,6 Monate [95 % CI 1,5-2,9 Monate]).

hepatic progression-free survival: s.s.

Das *(hepatisch-)objektive Ansprechen* zwischen den beiden Gruppen wies eine statistisch signifikante Verbesserung zugunsten der M-PHP-Gruppe auf (p<0,001). Die *objektive Ansprechrate* war in der M-PHP-Gruppe statistisch signifikant höher als in der Kontrollgruppe, mit einem p-Wert von p<0,01.

(hepatic) objective response rate: s.s.

Sicherheit

Es konnten keine Studien zu primären Leberkrebs identifiziert werden.

In der RCT wurden 4,3 % (n=4/93 Patient*innen) unerwünschte Ereignisse mit Todesfolge gemeldet, wovon drei *Todesfälle* auf M-PHP zurückzuführen waren (1 Studie). In der Beobachtungsstudie wurden keine Todesfälle gemeldet (1 Studie).

4 deaths (RCT), no deaths (case series)

Periprozessuale Ereignisse (Grad 3/4-Ereignisse) wurden in der RCT bei 90 % aller mit M-PHP behandelten Patient*innen (n=63/70 Patient*innen) beobachtet. *Postprozessuale Ereignisse* (Grad 3/4-Ereignisse) wurden bei 91,4 % (n=64/70 Patient*innen) beobachtet (1 Studie).

~90% peri and post-procedural events (grade 3) (RCT)

In der Beobachtungsstudie traten bei 14 (2 %) von 67 M-PHP-Behandlungen *schwerwiegende unerwünschte Ereignisse* auf. Was die *nicht-hämatologischen und nicht-hepatischen Komplikationen* betrifft, so traten Komplikationen aller Grade bei 58 (87 %) Behandlungen auf. Bei 14 (21 %) Behandlungen traten Komplikationen dritten Grades auf und bei einer (2 %) der 67 Behandlungen Komplikationen vierten Grades. *Hämatologische Spätereignisse (Grad 4)* traten auf wie z. B. Thrombozytopenie (11/62 Verfahren [17,7 %]), Leukopenie (22/62 Verfahren [35,5 %]) und Neutropenie (26/62 Verfahren [42,6 %]). *Hepatische Spätereignisse (alle Grade)* traten auf wie z. B. erhöhte Alanin-Aminotransferase (36/62 Verfahren [58,1 %]), erhöhte Aspartat-Aminotransferase (21/60 Verfahren [35,0 %]) und erhöhte Bilirubinwerte (6/60 Verfahren [10,0 %]), nicht jedoch Grad 3 oder 4 Ereignisse (1 Studie).

adverse and (non-)haematological/ hepatic events (case series)

In der RCT wurden bei zwölf Patient*innen (17,1 %) *periprozessuale Ereignisse* wie kardiale Toxizität gemeldet. *Postprozessuale Ereignisse* standen im Zusammenhang mit den Auswirkungen der Knochenmarksuppression (1 Studie).

17% cardiac toxicity (RCT)

In der Beobachtungsstudie traten keine *hepatischen Ereignisse* der Grade 3 und 4 auf, es wurde jedoch ein statistisch signifikanter Anstieg (p<0,01) der Aminotransferasen beobachtet, was auf ein gewisses Maß an hepatischer Toxizität hinweist (1 Studie).

s.s. increase of aminotransferases (case study)

In der RCT brachen 67 (95,8 %) von 70 mit M-PHP behandelten Patient*innen die Therapie ab, hauptsächlich aufgrund von unerwünschten Ereignissen und Fortschreiten der Erkrankung (1 Studie). In der Beobachtungsstudie wurde bei fünf (7,5 %) von 67 Verfahren ein *Therapieabbruch* beschrieben, hauptsächlich aufgrund von Filtergerinnung (1 Studie).

treatment discontinuation: 96% (RCT) and 8% (case series)

Laufende Studien

ongoing studies

Die Suche nach laufenden Studien ergab, dass es in den USA derzeit eine laufende RCT gibt, welche von Delcath Systems Inc. gesponsert wird. Diese Studie vergleicht die Wirksamkeit, Sicherheit und Pharmakokinetik von M-PHP, welche im Anschluss an die Cisplatin/Gemcitabin-Gabe verabreicht wird, versus nur Cisplatin/Gemcitabin-Gabe (Standardbehandlung) bei Patient*innen mit intrahepatischem Gallengangskarzinom (n=295). Die voraussichtliche Fertigstellung ist für Mai 2023 geplant.

Kostenerstattung

currently no reimbursement of M-PHP in Austria

Das Hepatic CHEMOSAT® Delivery System ist seit 2012 in Europa zugelassen und besitzt eine CE-Kennzeichnung. In den USA ist die Zulassung durch die Food and Drug Administration in Vorbereitung. In Österreich ist M-PHP derzeit nicht im Leistungskatalog (LKF, leistungsorientierte Krankenanstaltenfinanzierung) enthalten und somit keine voll erstattungsfähige Leistung. Deutschland ist das einzige europäische Land mit einer Kostenerstattung durch die Krankenkassen.

Diskussion

partly effective

M-PHP könnte hinsichtlich des Gesamtüberlebens und des hepatisch-progressionsfreien Überlebens wirksamer sein als beste verfügbare Behandlung. Es konnte keine Evidenz für die Lebensqualität identifiziert werden, und das Gesamtüberleben verbesserte sich durch die M-PHP im Vergleich zur besten verfügbaren Behandlung statistisch nicht signifikant.

overall survival: not s.s. possibly due to high crossover rate

Der fehlende Nachweis eines Vorteils von M-PHP hinsichtlich des Gesamtüberleben in der RCT könnte auf den hohen Crossoveranteil der Kontrollgruppe zurückzuführen sein, der einen möglichen Vorteil für das Gesamtüberleben zunichte gemacht haben könnte. Außerdem hatte eine nicht unerhebliche Anzahl von Patient*innen Metastasen außerhalb der Leber, was die optimale Wirkung der auf die Leber gerichteten Therapie möglicherweise einschränkt hat.

4 deaths

complications and treatment discontinuations

Drei von vier Todesfällen wurden auf M-PHP zurückgeführt. Bei der Mehrzahl der Patient*innen wurden verfahrensbedingte Komplikationen beobachtet, und viele brachen die M-PHP-Therapie ab. Die geringe Zahl der in die Studien einbezogenen Teilnehmer*innen könnte das Auftreten von Sicherheitsereignissen beeinflusst haben. Dies lässt sich jedoch durch die Seltenheit der Krankheit erklären. Außerdem wurden in den eingeschlossenen Studien Filter der Generationen 1 und 2 verwendet, was ebenfalls die Verallgemeinerbarkeit der Sicherheitsergebnisse beeinträchtigen kann.

NICE: toxicity and serious complications

Das Komitee des NICE-Leitlinie stellte fest, dass die Toxizität des Verfahrens in erster Linie davon abhängt, wie effizient Melphalan entfernt wird und daran gehindert wird, in den systemischen Kreislauf der Patient*innen zu gelangen. Außerdem kann die systemische Toxizität auf andere Faktoren und nicht nur auf eine unvollständige Filtration zurückzuführen sein. Unsere Ergebnisse stützen diese Argumentation, wonach die Evidenz für die Sicherheit von M-PHP schwerwiegende, erkennbare Komplikationen zeigen.

Empfehlung

partly effective, but serious complications

Die vorliegende Evidenz ist unzureichend und mit begrenzter interner und externer Validität, um den klinischen Nutzen von M-PHP bei Patient*innen mit sekundärem Leberkrebs im Vergleich zur besten verfügbaren Behandlung zu belegen. Die einzige RCT zeigte, dass M-PHP beim Gesamtüberleben und beim progressionsfreien Überleben der Leber wirksamer ist als beste verfügbare Behandlung. Das Gesamtüberleben wurde durch die M-PHP nicht statistisch signifikant verbessert. Es wurden jedoch schwerwiegende, erkennbare Komplikationen in Bezug auf die Sicherheitsergebnisse nachgewiesen.

evidence insufficient

Aufgrund der insgesamt sehr geringen Evidenzstärke und des hohen Verzerrungsrisikos der RCT können keine endgültigen Schlussfolgerungen zur Wirksamkeit von M-PHP im Vergleich zu bester alternativer Behandlung gezogen werden. Es fehlen weitere Ergebnisse aus gut konzipierten RCTs, und die Ergebnisse laufender Studien sind abzuwarten.

re-evaluation in 2024

Auf der Grundlage der verfügbaren Evidenz wird die Aufnahme von PHP bei sekundärem Leberkrebs in den Leistungskatalog derzeit nicht empfohlen. Neue Studienergebnisse werden die Effektschätzung möglicherweise noch beeinflussen. Die Re-Evaluierung wird 2024 empfohlen, wenn eine große RCT (>200 Patient*innen; NCT03086993) mit patientenrelevanten primären Outcomes publiziert ist.

1 Background

1.1 Overview of the disease, health condition and target population

1.1.1 Overview of the disease or health condition

Primary liver cancer

Leberzellenkarzinom (HCC): häufigster primärer Leberkrebs mit schlechter Prognose

Hepatocellular carcinoma (HCC), the most frequent form of primary liver cancer, is one of the most lethal cancers worldwide and is commonly caused by hepatitis infections (75%). Mortality rates are almost the same as incidences rates, and those patients' prognosis is dismal [1]. According to the German AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.) guideline, in 2018 worldwide, 841,000 individuals were affected by primary liver cancer, and more than 781,000 died from this diagnosis [19]. In Austria, in 2017, 1,040 malignant neoplasms of the liver were diagnosed, accounting for about 2.5% of the annual number of cancer cases [2]. Austrian data of 2019 indicates 1,025 malignant liver cancers were diagnosed in 2019 (760 in men and 265 in women), accounting for 2.5% of the annual cancer diseases in this year. In 2019, the age-adjusted incidence rate was 11.5 cases per 100,000 [3].[1]

selten, jedoch unter den 10 häufigsten Krebstodesursachen

mehr Männer betroffen

leichter Rückgang an Todesfällen von 2017 bis 2019

This disease is relatively rare, but due to its poor prognosis, it is one of the ten most frequent causes of cancer deaths in Austria (920 deaths in 2017, 4.5% of all cancer deaths). The age-standardised rates showed 10.7 deaths per 100,000 persons annually (in 2019: 9.7 deaths [3]); eleven out of every 100,000 persons died from malignant neoplasms of the liver. The proportion of men is generally above the average: In 2017 and 2019, around two-thirds of the annual new cases and of new cases and deaths from liver tumours were men. 1,368 men and 509 women with a malignant liver tumour were alive at the end of 2017. The relative 1-year survival rates increased from 2000-2004 to 2015-2017 from 30% to 44%, and the relative 5-year survival rates increased from 2010-2014 from 11% to 14% [2]. The mortality rate in 2019 in Austria was 867, which is a slight decrease compared to 2017 [3][2].

intrahepatisches Gallengangskarzinom: zweithäufigster primärer Leberkrebs

The second most common primary liver tumour is intrahepatic cholangiocarcinoma. This type of tumour affects the biliary epithelium, and the only curative treatment option is radical resection. However, multimodal treatment strategies are needed to improve the cure rate, as 5-year survival rates of only 25-30% are reported [1].

Secondary liver cancer

sekundärer (Lebermetastasen) häufiger als primärer Leberkrebs

Metastases to the liver (secondary liver cancer) are more common compared to primary liver tumours [1]. Even if the primary tumour is successfully treated, up to 50% of patients eventually develop metastatic diseases with predominant liver involvement [4]. In patients with only one site of metastasis, the

[1] **A0023** – How many people belong to the target population (primary liver cancer)?

[2] **A0005** – What is the burden of disease for patients with malignant neoplasms of the liver?

liver is involved in 95% of cases [5]. The predominant site of metastasis for a variety of primary tumour types such as colorectal cancer/carcinoma, ocular melanoma, and gastrointestinal neuroendocrine tumours is the liver [1, 6].[3]

1.1.2 Target population and effects of the disease on the individual

Zielgruppe: Patient*innen mit inoperablem primären oder sekundären Leberkrebs …

In this report, patients with unresectable liver cancer, i.e., primary liver cancer or secondary liver cancer (metastases spread to the liver from another part of the body), are assessed. Liver metastases from varying histologies, types of tumour or origin of the metastases are included, such as ocular or cutaneous melanoma origin, metastasis origin from any solid tumours, cholangiocarcinoma patients, primary or secondary liver tumours (ICD-10 codes: C22.0, C69.0, C69.3, C69.4, C78.0, C78.7).[4]

… verschiedenster Arten

The assessed intervention, percutaneous hepatic perfusion (PHP), is performed in patients with primary liver cancer and hepatic metastases from sarcomas, neuroendocrine tumours, and various types of carcinomas [7], but also in patients with HCC or cholangiocellular carcinoma, liver-limited diseases and extra-hepatic cancer [1].[5]

Primary liver cancer

Risk factors[6]

Risikofaktoren: Leberzirrhose, Hepatitis, Alkohol, Diabetes, Adipositas, etc.

According to German guidance, the most common risk factors for primary liver cancer (most commonly HCC) are liver cirrhosis, chronic hepatitis B and C virus infection and alcohol consumption, followed by diabetes and adiposity. The incidence of HCC in the Western world has significantly increased due to chronic hepatitis C virus infection-related liver cirrhosis as well as the marked increase in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty liver hepatitis (NASH) with advanced fibrosis or cirrhosis [19]. In 2018, 53% of liver cancers in Austria were attributed to both hepatitis B and C combined [8].

Fettleber als häufigster Risikofaktor in westlichen Ländern

Based on the prevalence of NAFLD, this risk factor is expected to be the most common HCC trigger in the Western world in the next decade. Type 2 diabetes doubled the risk of progression to NALFD, and mortality risk increased with disease stage [19]. Males have a higher risk for HCC than females, and the risk increases with age [9].

[3] **A0005** – What is the burden of disease for patients with metastatic diseases?

[4] **A0007** – What is the target population in this assessment?

[5] **A0001** – For which health conditions, and for what purposes is percutaneous hepatic perfusion used?

[6] **A0003** – What are the known risk factors for hepatocellular carcinoma (primary liver cancer)?

Secondary liver cancer

meisten perkutanen Leberperfusionen mit Melphalan (M-PHP) bei Lebermetastasen durch Augenmelanom

In Europe, in 2016, most melphalan percutaneous hepatic perfusion (M-PHP) procedures were performed and investigated in patients with hepatic metastases from ocular melanoma (n=213) [1], but also from uveal melanomas [7]. According to the submitting Austrian hospital, in 2020, seven M-PHP were performed. The annual frequency at Austrian institutions is estimated to be 40 procedures.[7] Hepatic metastases from ocular, uveal, and cutaneous melanoma are the diseases in the scope of this assessment.[8]

Hepatic metastases from ocular and cutaneous melanomas

Augenmelanom: oft Aderhaut betroffen; Lebermetastasen durch Hautmelanom am zweithäufigsten

Ocular melanoma is, after cutaneous melanoma, the second most common type [4, 10]. Ocular melanoma can be divided into non-uveal and uveal ocular melanoma; the latter is more frequent [10]. Ocular melanoma frequently arises from melanocytes in the uveal tract or develops in the conjunctiva [4]. The majority of ocular melanomas originate from the uvea, while conjunctival melanomas are less frequent [11].

***nur* Leber in ~50 % der Fälle betroffen; Leber in 89 % predominant**

In patients with ocular melanoma, the liver is the most common *sole* site of metastatic diseases (up to 50%) after primary cancer treatment [6, 12]. The clinical course of ocular and cutaneous melanomas distinctly differs. In 89% of patients with ocular melanoma developing metastases, the liver is the predominant metastatic site. Ocular melanoma spreads hematogenously and, therefore, liver metastases are common. In comparison, only 10-20% of patients with metastases from cutaneous melanoma develop liver and bowel metastases [13].

bei Hautmelanomen nur 10-20 %

schlechte Prognose aufgrund eingeschränkter Therapiemöglichkeiten

Hepatic metastases from melanoma are, regardless of the primary tumour type, a crucial determinant of the survival and clinical course of the affected patients [13]. The median survival rate is estimated to be less than nine months in patients with metastatic ocular melanoma [6]. Ocular melanoma comprises 3-4% of all melanomas in the United States of America (USA). Once liver metastases occur, it carries a very poor prognosis as no established, effective alternative or systemic locoregional treatments exist [4, 10, 12, 14].[9]

Hepatic metastases from uveal melanomas

Inzidenz von Aderhautmelanom in Nordeuropa höher …

The most common primary intraocular malignancy in adults is uveal melanoma, representing 3-5% of all melanomas [5, 15]. Men have a 30% greater incidence than women [15]. In Europe, the incidence of uveal melanoma is approximately 4.4 cases per million between 1995 and 2002 [16], and two to eight per million per year in Caucasians [17]. The incidence varies with the geographical latitude, as it is higher in North Europe (≥8 per million) than in South Europe (<2 per million) [17].[10]

… aufgrund positiver Assoziation mit kaukasischer Ethnizität

This difference is due to a positive association with light eye colour, fair skin, and Caucasian ethnicity [17]. Further risk factors for uveal melanoma include congenital ocular melanocytosis and neurofibromatosis, but the role of sun-

[7] **A0011** – How much is percutaneous hepatic perfusion utilised?

[8] **A0002** – What is the disease or health condition in the scope of this assessment?

[9] **A0004** – What is the natural course of hepatic metastases from cutaneous and ocular melanomas?

[10] **A0023** – How many people belong to the target population (hepatic metastases from uveal melanomas)?

light is still uncertain. Familial cases are very rare [15, 17]. Diagnosis is mainly established after age 50 [4], and at approximately 60 years, the age at presentation peaks, except for iris melanomas usually present in younger generations [17].[11]

in ~50 % der Fälle Metastasenbildung, davon in ~90 % Leber betroffen

natürlicher Verlauf mit schlechter Prognose

In patients with uveal melanoma, a high risk (up to 50%) of developing metastatic disease exists [16, 18]. This frequent development of metastases characterises the natural cause of uveal melanoma, occurring at any time of the disease stage [17]. The liver is the most common and frequently affected site for distant uveal melanoma metastases with up to 90% involvement [5, 17, 18]. 50% of patients have liver-only diseases, and 90% have metastases elsewhere plus liver metastases [5]. The skeleton and lungs can be mentioned as other common metastatic sites [18]. The cause of death in most patients with metastatic uveal melanoma is liver involvement [5, 17, 18] (93% had liver metastases at the time of death), impacting survival and patients with poor prognoses [5, 16].[12]

Risikofaktoren für metastatischen Rückfall

Überlebenszeit und Metastasenentwicklung

The risk of metastatic relapse varies depending on genetic alterations and primary tumour characteristics. Outcomes are poor once metastatic disease from uveal melanoma occurs [17]. The median survival from the time when developing distant metastatic diseases is two to 12 months, and one-year survival ranges from 10-15% [17]. 25-31% of the patients are developing metastases within five years, 34-45% within 10-15 years, and half of them within 25 years [18]. Within five years of diagnosis, 20-30% of patients with uveal melanoma died of systemic metastases. This figure will rise to 45% within the next 15 years [5].

Einstufungssystem bei Augenkrebs

gratis online tool

The American Joint Committee on Cancer (AJCC) Tumour-Node-Metastasis (TNM) staging system for eye cancer performs the staging for uveal melanoma. The outcomes for patients with uveal melanoma vary, but outcomes are excellent for those with early tumours. The Liverpool Uveal Melanoma Prognosticator Online (LUMPO), a freely available online tool, generates an all-cause mortality curve for patients according to different variables such as sex, age, melanoma cytomorphology, or presence of extraocular spread (www.ocularmelanomaonline.com) [17].

[11] **A0003** – What are the known risk factors for hepatic metastases from uveal melanomas?

[12] **A0004** – What is the natural course of hepatic metastases from uveal melanomas?

1.2 Current clinical practice and management of the disease or health condition

1.2.1 Diagnosis of primary liver cancer[13]

Vorsorgeuntersuchung und Screening zur Früherkennung z. B. Ultraschall, Leberbiopsie

Preventive medical checkups and screenings for early detection are crucial in diagnosing primary liver cancer. Patients with liver cirrhosis or risk factors should participate in HCC screening; an ultrasound examination of the liver should be performed every six months. The sensitivity of screening is increased by an additional alpha-fetoprotein (AFP) determination. Furthermore, liver biopsy is an important diagnostic measure for diagnosing HCC [19].

chronische Patient*innen: Fibrosestadium-untersuchung

In patients with chronic liver disease, the fibrosis stage should be repeatedly assessed to better evaluate the risk of HCC. The typing of HCC should follow the current WHO classification. Molecular pathology assessments can be used to support tumour typing and dignity determination of hepatocellular tumours. Early HCC detection aims to diagnose the disease at an early stage and thus reduce mortality through effective treatment methods [19].

1.2.2 Management of the disease[14]

endovaskuläre Therapien

Treatment of primary or secondary liver cancer depends on the stage and location and how much liver function is preserved [19]. A range of endovascular therapies is available to treat primary and metastatic hepatic malignancy, such as chemoembolisation using different chemotherapy agents, bland arterial embolisation, radioembolisation or immunoembolisation [5].

primärer Leberkrebs z. B. Transplantation, Resektion, transarterielle Chemoembolisation

In patients with early-stage disease of *primary* liver cancer, potentially curative treatments are liver transplantation, resection, and microwave or radiofrequency ablation. Transarterial chemoembolisation (TACE) is recommended for patients with intermediate-stage. The agent sorafenib is used for advanced disease, as HCC is typically resistant to systemic chemotherapy [1].

inoperabler Leberkrebs: intra-arterielle und hyperthermische Therapien

The current clinical management of *unresectable* primary and secondary liver cancer can be divided into intra-arterial and hyperthermic therapies. Intra-arterial therapies include, e.g., hepatic artery infusion (HAI), TACE, selective internal radiotherapy (SIRT) and immunoembolisation (IE). Hyperthermic therapies include, e.g., radio frequent ablation (RFA) and laser-induced interstitial thermotherapy (LITT) [18].

sekundärer Leberkrebs: Chemotherapie

There is a strong predilection for hepatic involvement; therefore, liver-directed therapies represent a crucial research focus in metastatic disease treatment [5]. In patients with *metastatic* disease, chemotherapy improves survival and quality of life. The standard of care represents the chemotherapy combination gemcitabine with cisplatin. However, clinical trials of better and new agents are needed as patients ultimately progress on this therapy combination [1].

The following describes liver surgery, systemic and regional therapies in further detail, used in the treatment of metastatic melanoma to the liver:

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[13] **A0024** – How is primary liver cancer (hepatocellular carcinoma) currently diagnosed according to published guidelines and in practice?

[14] **A0025** – How are primary and secondary liver cancer currently managed according to published guidelines and in practice?

Liver surgery

chirurgische Leberentfernung …

Surgical resection might be a curative option in patients with isolated hepatic metastases. But in most patients, complete resection is not possible due to the number, location or size of hepatic metastases. Furthermore, resection is limited by poor hepatic functional reserve [6].

… verlängert Überlebenszeit

Hepatic resection promises a longer duration of overall survival (14-24 months) compared to non-surgical care (3-12 months) in patients with ocular melanoma. A similar trend can be observed in patients with cutaneous melanoma, where liver metastases are less common (28 vs 6 months) [13].

Systemic therapy

Chemotherapie …

Surgery is offered only 2-7% of patients with liver metastases from melanoma, and alternative treatment options are provided to the remaining patients with unresectable diseases [13]. For these patients, systemic chemotherapy is commonly the first therapeutic intervention. The response rate ranges from 35-60% and median survival times from 15 to 27 months [12]. Several approved novel therapies exist for patients with metastatic cutaneous melanoma [13].

… für Patient*innen mit Augenmelanom limitiert

In patients with metastatic ocular melanoma, the response rate is low, generally ≤5%, with an overall survival duration from 6-14 months, although a wide range of immunomodulatory and chemotherapeutic agents have been tested [13]. Therefore, systemic therapy is limited in number and efficacy for these patients, often presenting unresectable liver metastases [7, 12].

Regional therapies

lebergerichtete regionale Therapien mit begrenzter Toxizität …

Regional therapies, also known as liver-directed treatments, deliver dose-intensive therapy to the liver while limiting unnecessary systemic toxicities. They have an increasingly crucial role in managing unresectable liver metastases [12]. Regional therapies are applied to the liver directly and can be seen as minimally invasive techniques. A gradual shift from surgeries to regional therapies reduced morbidity. The advantage is that regional therapies can be delivered to both radiographically and clinically evident tumours and clinically occult micrometastases, while unwanted systemic toxicity is limited [13].

… über Leberarterie eingeführt

Importantly, hepatic metastases derive blood supply almost exclusively from the hepatic artery (vs portal vein). Therefore, the hepatic artery is used for injection to selectively deliver regional therapies to the liver [20]. Regional treatments include hepatic arterial infusions, chemoembolisation, and isolated (IHP) or PHP [13].

Hepatic arterial chemotherapy

arterielle Leberchemotherapie

In hepatic intra-arterial chemotherapy, catheters are introduced into the hepatic artery either percutaneously via the femoral artery or surgically via the gastroduodenal artery. Patients receive on average eight treatments with implantable catheters or 3-4 treatments via temporary catheters. The agents most widely used are fotemustine, melphalan and cisplatin [13].

Hepatic arterial chemoembolisation

arterielle Leberembolisation

This technique is commonly employed in delivering high-dose chemotherapy directly to liver tumours. The advantage is that chemotherapy dwell time increases. TACE, which is mostly involved, uses various chemotherapeutic agents for this technique. A key prognostic factor in patients treated with TACE is the extent of liver involvement [13].

Isolated and percutaneous hepatic perfusion

isolierte Leberperfusion …

In treating hepatic metastases, isolated or percutaneous techniques can be used for liver perfusion with chemotherapeutic agents [13]. IHP is an open-surgical alternative [1]. For IHP, delivering high doses of chemotherapy directly to the organ is allowed due to the surgically isolated vascular supply to the liver [13]. It is a liver-directed therapy with melphalan and was first applied 60 years ago to treat liver metastases [18].

… vs. perkutane Leberperfusion: minimal-invasiv und wiederholbar

The most frequently tested agent in hepatic metastasis from melanoma is melphalan. IHP is not widely used and only tested in specialised centres [13]. IHP was further developed to PHP with significant methodological improvements [21]. The difference between IHP and PHP is that PHP is a minimally invasive technique, and the procedure can be repeated [18].

1.2.3 Clinical guidelines[15]

deutsche S3-Leitlinie zu Melanomen 2020

In Germany, the 'Guideline on the diagnosis, treatment and follow-up care of melanoma' [S3-Leitlinie Diagnostik, Therapie und Nachsorge des Melanoms] was published in 2020 by the Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF), Deutschen Krebsgesellschaft e.V. (DKG) and Deutschen Krebshilfe (DKH) [21].

keine Empfehlung zu PHP

The AWMF clinical practice guideline mentioned PHP as a local therapeutic procedure, but there is no recommendation given yet ("Empfehlung offen").

bei Lebermetastasen:

The section ‚therapy of *liver metastases*' recommends:

- resection of liver metastases (recommendation level B[16], level of evidence 4[17]), including total metastasectomy **Resektion von Lebermetastasen oder**
- local therapeutic procedures (*recommendation level* 0[18], level of evidence 1b[19] and 4) including isolated hepatic perfusion, *PHP*, ablation, infusion, hepatic intra-arterial chemotherapy and chemoembolisation, radioembolisation/selective internal radiotherapy (SIRT), and/or embolisation strategies [21]. **lokale Therapieverfahren z. B. perkutane Leberperfusion**

keine grundlegende Prognoseverbesserung und therapeutische Standardtherapie

PHP has shown clinical response in trials but no fundamental improvement in prognosis and may be used depending on the number of metastases and their location [21]. Furthermore, a recently published German study states that no therapeutic standards exist so far for patients with unresectable tumours refractory to systemic therapies [14]. The procedure concept is not yet established in daily clinical practice [1].

---

[15] **A0025** – How are unresectable tumours currently managed according to published guidelines and in practice?

[16] "Recommendation" [21]

[17] "Case series (and qualitative poor cohort and case-control studies)" [21]

[18] "Recommendation open → can be used" ("Empfehlung offen → kann verwendet werden") [21]

[19] "Single RCT (with narrow confidence interval)" [21]

1.3 Features of the intervention: percutaneous hepatic perfusion

Features of the technology and comparators

perkutane Leberperfusion bei primären und sekundären Lebertumoren …

The medical device Hepatic CHEMOSAT® Delivery System is used for the treatment of patients with surgically unresectable

- primary liver tumours or
- secondary liver tumours (hepatic metastases from solid organ malignancies) [1].

… im Vergleich zu bestmöglicher Behandlung

For this report, M-PHP is compared to best available care, e.g., systemic chemotherapy, embolisation, supportive care (see Table 1-1).[20]

Alternative zu operativen Behandlungen

This system has been developed as an alternative non-operative treatment from Delcath Systems Inc., New York [13]. In 1994, the first use of PHP was reported [18], and in 2016, 186 patients received M-PHP treatments in the European Union [1].

Hepatic CHEMOSAT® Delivery System

Table 1-1: Features of the intervention and comparators

	Intervention/Technology	Comparator (reference codes in catalogue of benefits)
Name	Percutaneous hepatic perfusion	Best available care, e.g., systemic chemotherapy (XC204, XC380, XC820), chemoembolisation (XC280, XC284, XC296, XC444), transarterial chemoembolisation (TACE; ED050), supportive care
Proprietary name	Hepatic CHEMOSAT® Delivery System	
Manufacturer	Delcath Systems Inc., Queensbury, NY, USA	
Names in other countries	USA: HEPZATO™ KIT (melphalan hydrochloride for injection/hepatic delivery system)[21]	
Reference codes in catalogue of benefits	NA	
Class/GMDN code	Class IIb	

Abbreviation: NA – not applicable.

wiederholbar und minimal-invasiv

Chemosaturation with PHP represents a repeatable and less invasive alternative (requiring only percutaneous access) compared to isolated hepatic perfusion (IHP) [4, 5, 12]. The liver is isolated from the systemic circulation and directly and subsequently perfused with a high dose of melphalan, a chemotherapeutic agent; therefore, systemic exposures are limited [1, 4]. This regional treatment aims to destroy cancer using a very high dose of melphalan without causing side effects in the rest of the body [19].[22] Melphalan as the chemotherapeutic agent was selected for use with PHP due to its efficacy and reversible hepatic toxicity in treating hepatic metastases from various tumour types [1].

Melphalan-Perfusion der isolierten Leber …

… dadurch *limitierte* chemotherapeutische Belastung …

[20] **B0001** – What is the technology and the comparator?

[21] "HEPZATO™ has not been approved by the U.S. Food & Drug Administration. It is under evaluation in a global registration trial (single-arm, multi-centere, open-label FOCUS Trial) for treatment of patients with hepatic dominant ocular melanoma." see https://www.delcath.com/our-therapy/ (access date 31/01/2022)

[22] **B0002** – What is the claimed benefit of the intervention (melphalan chemosaturation with percutaneous hepatic perfusion)?

… aber nicht vollständig

However, in contrast to IHP, in PHP, some leak of the therapeutic agent into the systemic circulation occurs because the vascular isolation of the liver is not achieved completely. Therefore, systemic toxicities from the therapy can be clinically significant due to this incomplete isolation of the blood flow to the liver [12].

Filter: Generation 1 und 2

To reduce high rates of hematologic toxicity, a new hemofiltration system with a second-generation detoxification cartridge was developed. The original first-generation filter was modified to a second-generation filter, which became available in 2012 [4, 7, 12]. Pharmacological studies examined that the mean melphalan extraction rate of the second-generation filter (hemofiltration system) is 86% [4, 7] to 90% [6], which is approximately 10% higher than the rate of the first-generation filter [4, 7].[23]

NL: Erstlinien-Therapie bei metastasiernden Augenmelanomen

Recently, M-PHP has been adopted as a first-line treatment for patients with metastatic ocular melanoma in the Netherlands. This type of melanoma is often present with unresectable liver metastases, and there is a lack of effective systemic therapies [7].

In short, in M-PHP,

Melphalan-Perfusion der isolierten Leber bevor gefiltertes Blut in Blutkreislauf zurückkehrt

- the liver is endovascularly isolated from the circulation (minimally invasive),
- perfused with a chemotherapeutic agent (melphalan) through a catheter in the arterial system, and then
- the extracorporeally filtered blood is returned to the systemic circulation [13, 18].

Current approval status

CE-Zertifikat

seit 2012 zugelassen in UK, Deutschland, Niederlande, Italien und (Spanien), nicht aber in den USA

Since 2012, the Hepatic CHEMOSAT® Delivery System and related accessories, including the second-generation filter, have been approved and commercially launched in Europe for chemosaturation with PHP. It holds a CE marking (CE certificate Number CE 588215) regarding design, development, and manufacture. The Hepatic CHEMOSAT® Delivery System is commercialised in the UK, Germany, Netherlands, Italy and (Spain). In the USA, the Food and Drug Administration (FDA) has not approved the use of chemosaturation with PHP [6].

Verwendung des Systems für perkutane Leberperfusion

As stated in the CE certificate, the Hepatic CHEMOSAT® Delivery System and related accessories are used for percutaneous intra-arterial administration of chemotherapeutic agent (melphalan hydrochloride) to the liver with subsequent extracorporeal filtration of the regional (hepatic) venous blood, lowering the concentration of chemotherapeutic agent in the blood before returning it to the systemic venous circulation.[24]

[23] **B0003** – What is the phase of development and implementation of melphalan chemosaturation with percutaneous hepatic perfusion?

[24] **A0020** – For which indications has the Hepatic CHEMOSAT® Delivery System received marketing authorisation or CE marking?

Procedure in detail

Vorbereitungen: Anäshesie, Katheter in Leberarterie

Monitoring

First, general anaesthesia is performed with heparin-induced systemic anticoagulation after catheterisations to prevent blood clotting. A microcatheter is placed into the hepatic artery at the intended infusion location. Arterial and venous pressure, temperature, heart rate, and acid-base profile must be continuously monitored throughout the procedure, which takes three to four hours [1, 4, 6].

Isolation der Leber durch Doppel-Ballon-Katheter

A double-balloon catheter (Isofuse Isolation Aspiration Catheter, Delcath Systems Inc., New York) is placed in the inferior vena cava via the right common femoral vein to isolate and collect the hepatic venous outflow. This extracorporeal circuit is established stepwise: A closed loop is created using a centrifugal pump between the double-balloon catheter and the jugular sheath to maintain flow. The caudal and cranial balloons are inflated, prohibiting melphalan leakage into the systemic circulation [1, 4, 6, 12].

Angiographie prüft Isolation

Prior to chemotherapy, contrast angiography is obtained of all isolated sections confirming the absence of leakages and verifying isolation from the systemic circulation [6].

Leberperfusion mittels Melphalan

When the extracorporeal circuit is established, and the blood flow is stable, melphalan is administered via the catheter in the hepatic artery for 30 minutes. The melphalan high-dose of 3mg/kg (maximum dose of 200 mg) is infused through catheters placed between the two ballons [1, 4, 6, 12].

externer Blutfilter bevor zurück in Blutkreislauf

To lower the melphalan concentration, the hepatic venous outflow is sent through a filtration system outside the body (30 minutes) before the filtered blood is returned via the right internal jugular vein to the systemic circulation [1, 4]. This filtration allows a complete melphalan washout in the liver [4, 6].

Hypotonie während Behandlung

At two points during the procedure, patients will experience hypotension. First, when the venous balloons are inflated and, second, when the filters in the bypass circuit are activated. During the treatment, blood pressure is decreased using vasoactive drugs and intravenous fluids until the pressure normalises [1, 6].

Katheterentfernung

Monitoring und Entlassung der Patient*innen

After the PHP procedure, protamine is used to reverse heparin, which was used for anticoagulation. When blood values and coagulation have normalised, intravascular access sheaths and catheters are removed [1, 6]. Patients are monitored for six to 24 hours at an intermediate or intensive care unit and then for two to three days on a general ward. Usually, they are discharged home on the postoperative day. Postoperative monitoring assesses twice-weekly laboratory studies (i.e., renal and hepatic function tests, complete blood count) for up to four weeks [1, 6].

Zusammenfassung des Behandlungsprozesses

To summarise this process (see Figure 1-1, [6]):

- A catheter is percutaneously placed in the hepatic artery.
- A double-balloon catheter is placed in the inferior cava vein. The given isolation prevents leakage of melphalan to the systemic circulation.
- Between these balloons, blood is aspirated coming from the hepatic veins.
- Melphalan is administered into the proper hepatic artery (via femoral artery) for the infusion of chemotherapy.
- Blood runs through the extracorporeal filter system for melphalan washout.

- Blood runs back to the patient's circulation through a third catheter in the jugular vein, and the filtered blood is returned to the systemic circulation [18].

schematische Übersicht der Komponenten

Figure 1-1 illustrates a schematic overview of how the Hepatic CHEMOSAT® Delivery System components work together. A complete setup for PHP is shown: drug delivery (yellow highlighted, via left femoral artery catheterisation into the hepatic proper artery); normal saline for priming (A); removal of melphalan-infused blood from the retrohepatic inferior vena cava double-balloon catheter (B and C); bypass and filtration (D to E); and the return line (F) [6].

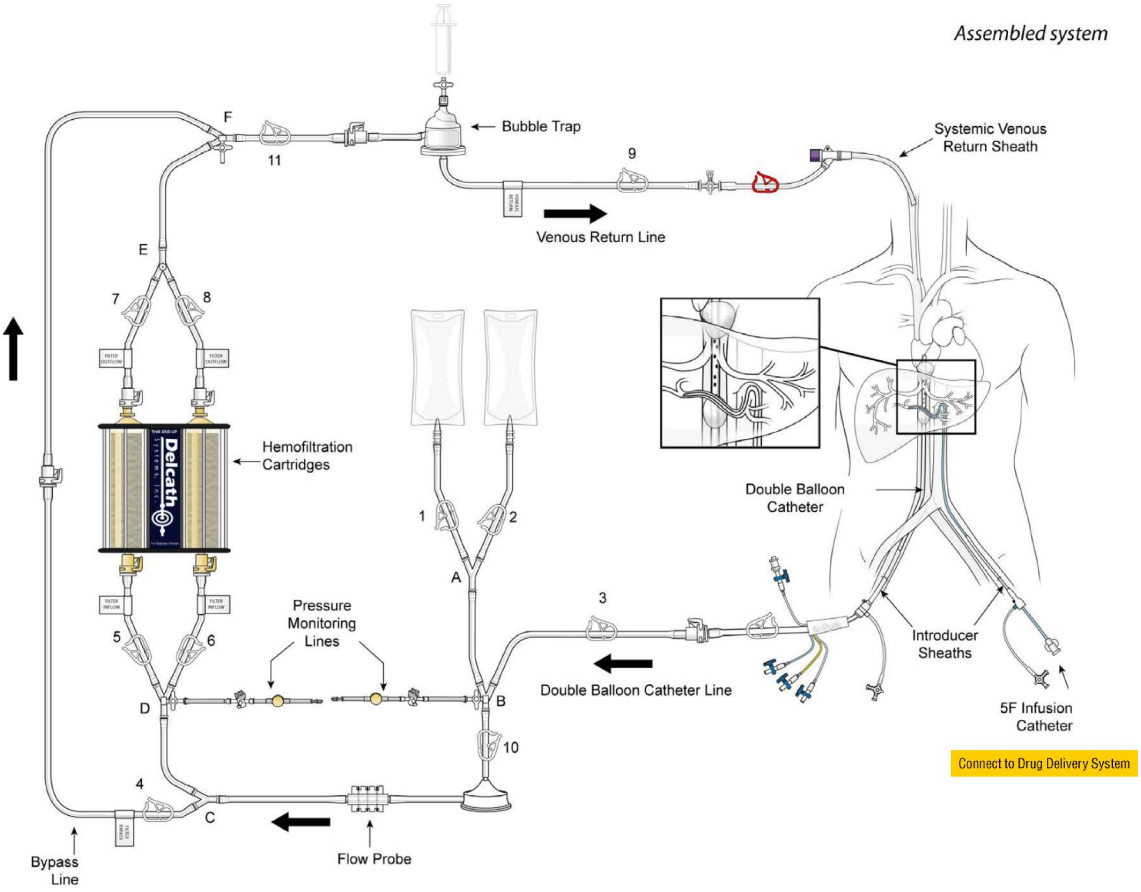

Figure 1-1: Illustration of percutaneous hepatic perfusion (PHP) using the Hepatic CHEMOSAT® Delivery System [6]

Administration, investments, personnel and tools required to use the technology and the comparator(s)

multidisziplinäres Team und spezielle Räumlichkeiten erforderlich

Performing the PHP procedure requires a multidisciplinary team. The entire procedure team is led through coordination and communication by an interventional radiologist. A medical or surgical oncologist is responsible for managing the patient, i.e., prior to the procedures through follow-up. An anesthesiologist is responsible for general anaesthesia, coagulation management, and postoperative care and monitors vital signs throughout the procedure. The extracorporeal circuit is established, monitored, and controlled by a perfusionist. An interventional radiology staff assists in proceeding and imaging, and

a pharmacist is responsible for preparing melphalan [1].[25] Chemosaturation with PHP is performed in interventional radiology suites or operating rooms with fluoroscopic imaging capability [6, 12].[26]

Komponenten des Hepatic CHEMOSAT® Delivery Systems …

The medical device Hepatic CHEMOSAT® Delivery System is used to perform the locoregional therapy chemosaturation PHP [1]. The system comprises several single-use, sterile components, i.e., an extracorporeal circuit with hemofiltration cartridges and catheters [1]. This closed circuit of drug-specific filters and catheters is utilised to deliver melphalan to the (hepatic) artery of the liver. Before the blood is returned to the systemic circulation, melphalan concentration is lowered [22].

… im Detail

The system consists of the following components [22]:[27]

- Delcath Isofuse® Isolation Aspiration Catheter
- Accessory Pack
- 5F Chemofuse® Chemo Delivery Catheter
- Delcath Hemofiltration (Chemofiltration)Dual Filter Cartridge (Chemofilter)
- Hemofiltration (Chemofiltration) Circuit (“Extracorporeal Circuit”)
- Carbon Dioxide (CO^2) Connection Line

Supplied disposable components are presented in Figure 1-2 [22].

Regulatory & reimbursement status[28]

CE-Zertifizierung in Europa, nicht jedoch in den USA

As mentioned above, the Hepatic CHEMOSAT® Delivery System has been approved in Europe since 2012 and holds a CE marking. In the USA, FDA approval is being prepared.

in Österreich keine Kostenrückerstattung von M-PHP, jedoch in Deutschland

In Austria, M-PHP is currently not included in the catalogue of benefits (LKF, leistungsorientierte Krankenanstaltenfinanzierung) and, hence, it is not a fully reimbursable service. Germany is the only European country with reimbursement by health insurance (Diagnosis Related Groups [DRG] plus individually negotiated additional charge ZE2022-117). On the 21st of April 2021, the status in the UK was changed by the independent interventional procedures advisory committee (IPAC) from NICE: from Research Only Status to Special Arrangements Status, which can be seen as the basis for negotiations with health insurances to pay the costs.[29]

[25] **B0004** – Who administers percutaneous hepatic perfusion and in what context and level of care are they provided?

[26] **B0008** – What kind of special premises are needed to use percutaneous hepatic perfusion?

[27] **B0009** – What supplies are needed to use percutaneous hepatic perfusion?

[28] **A0021** – What is the reimbursement status of the technology?

[29] Anja Matz (Medical Science Liaison Manager, Delcath Systems GmbH, Germany), personal communication 02/02/2022

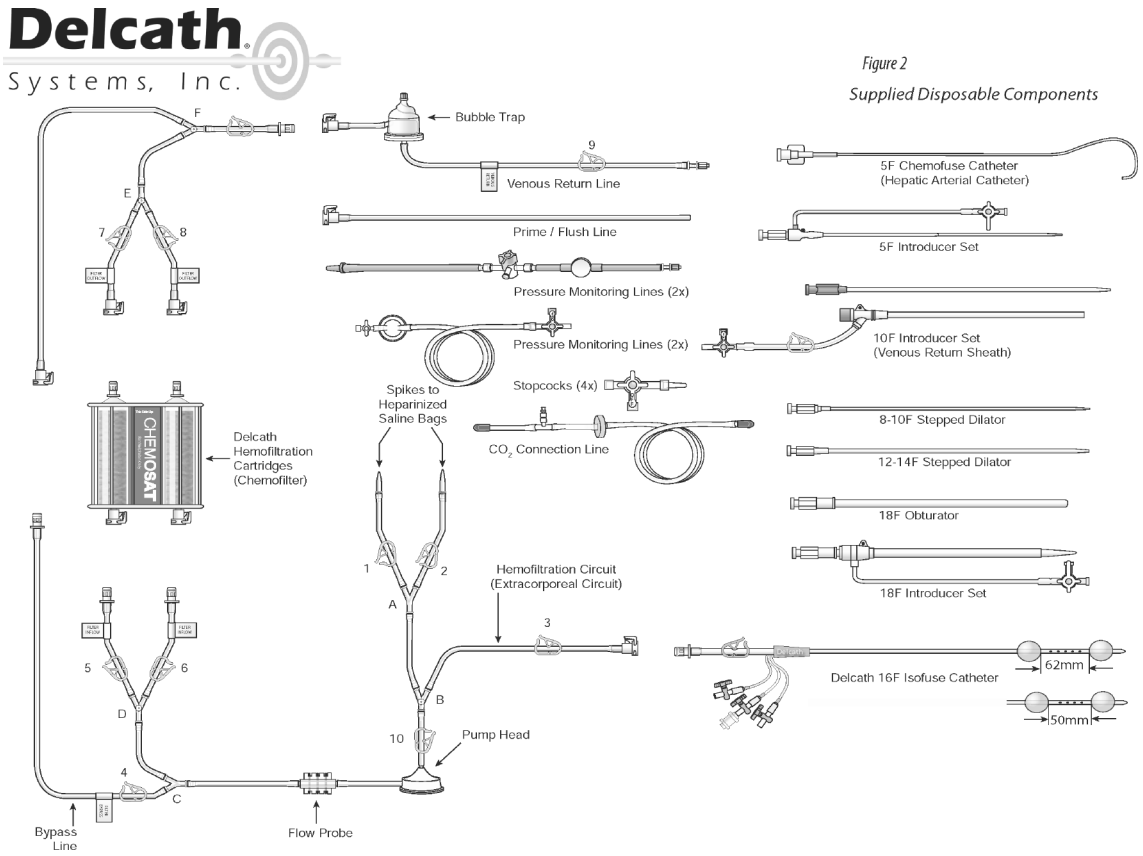

Figure 1-2: Supplied disposable components [22]

2 Objectives and scope

2.1 PICO question

PIKO-Frage

Is M-PHP in comparison to best available care in patients with unresectable primary or secondary liver cancer more effective and safe concerning efficacy (i.e., overall survival, quality of life, progression-free survival, and tumour response), and safety (i.e., procedure-related complications, bone marrow or haematological toxicity, and death)?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

Population	Patients with unresectable **primary or secondary** (metastases to the liver) liver cancer[30] Type of tumour/origin of the metastases: e.g., metastasis origin from any solid tumours, ocular or cutaneous melanoma, cholangiocarcinoma patients ICD-10 codes: C22.0, C69.0, C69.3, C69.4, C78.0, C78.7
Intervention	Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation[31] as last-line[32] treatment (non-surgical treatment) For chemosaturation used product: first-/second-generation of the **Hepatic CHEMOSAT® Delivery System** (Delcath Systems Inc., Queensbury, NY, USA)
Control	Best available care, e.g., systemic chemotherapy, embolisation, supportive care
Outcomes	
Efficacy	■ Overall survival ■ Quality of life ■ Progression-free survival ■ Tumour response (hepatic objective response) ■ Rationale: informed by other systematic reviews [19]
Safety	■ Procedure-related complications ■ Toxicity incl. bone marrow or haematological toxicity ■ Death ■ Discontinuation of therapy ■ Rationale: informed by other systematic reviews [19]
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case series (n ≥ 10)

[30] Rationale: Same population as in NICE guidance 2021 [19].

[31] Rationale: Same intervention as in NICE guidance 2021 [19].

[32] See [23]

3 Methods

3.1 Research questions

EUnetHTA Core Model®

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to this assessment's specific objectives [24].

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

NICE: systematische Übersichtsarbeit

We could identify a systematic review from NICE [19] with the same research question via hand search, which we critically appraised in AMSTAR 2, resulting in low overall confidence (see 3.2.3). This review was used to identify relevant studies. In addition, a systematic literature search for (non-)randomised controlled trials and prospective case series was conducted for the time period not covered by the selected review.

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on 16/12/2021 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

160 Zitate identifiziert

According to this review from NICE, which included studies until 12/2020, the systematic update search was limited to the search period 12/2020 to 12/2021 [19]. However, the publication period was from inception to December 2021. Furthermore, the search was limited to articles published in English or German, excluding conference abstracts. After deduplication, overall 160 citations were identified. The specific search strategy employed can be found in the Appendix (see Literature search strategies).

2. systematische Literatursuche

Additionally, a second systematic search was applied to identify systematic reviews and meta-analyses (available on request). Seventy articles could be found, and their reference lists were searched for relevant literature, whereof one article was identified.

Publikationen von Hersteller

Manufacturers from the medical device Hepatic CHEMOSAT® Delivery System submitted 13 publications, of which two new citations were identified.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries was conducted on 18/01/2022, resulting in 93 potential relevant hits, of which one relevant randomised controlled trial (RCT) could be identified (see Table A-8).

3.2.2 Flow chart of study selection

Literaturauswahl

Overall, 160 hits were identified through the systematic literature search. We further identified 11 studies from the NICE guidance, one study through the second systematic search, and two from the manufacturer. The publication period for the present report was from inception to December 2021 (search period: 12/2020 – 12/2021). Two independent researchers (LG, CW) screened the references, and in case of disagreement, a third researcher was involved in solving the differences. The selection process is displayed in Figure 3-1.

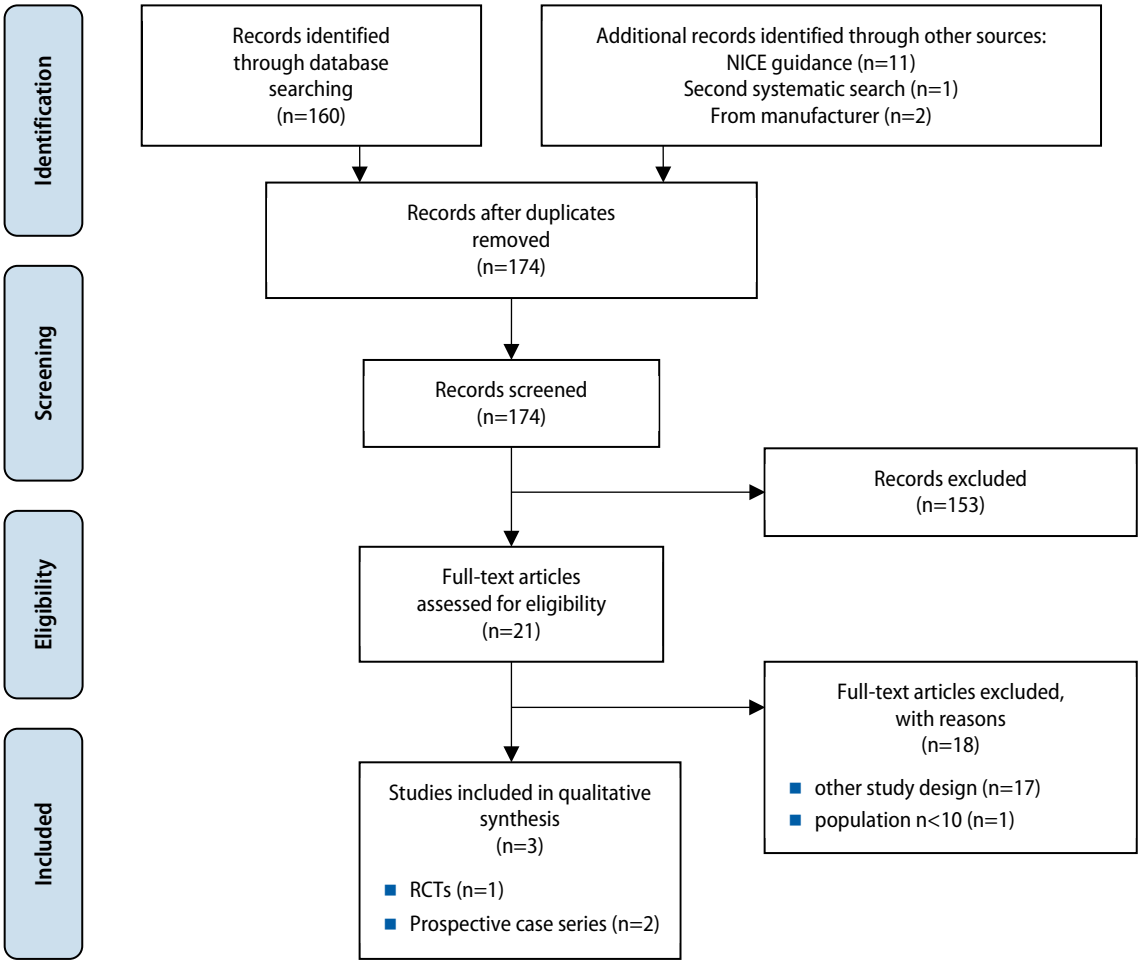

Figure 3-1: Flow chart of study selection (PRISMA flow diagram)

3.2.3 Analysis

Qualitätsbewertung der NICE Leitlinie

Two independent researchers (LG, CW) critically appraised the NICE guidance [19] in a blinded manner using the AMSTAR 2 tool [25] (see Appendix, Table A-1), which resulted in low overall confidence.

Datenextraktion und Kontrolle

The data from the selected studies were systematically extracted into data extraction tables (see Appendix, Table A-2 and Table A-3). The single-data extraction method with verification by another researcher was used: One researcher (LG) extracted the data, and one further researcher (VH) controlled the extracted data. No further data processing (e.g., indirect comparison) was applied.

Bewertung von Studienqualität und Verzerrungsrisiko

Studies were systematically assessed for internal validity and risk of bias (RoB) by two independent researchers (LG, VH). The 'Cochrane Collaboration's tool' version 2 [26] and the 'Institute of Health Economics (IHE) RoB checklist' [27] were used for assessing the RoB for RCTs and case series, respectively, as presented in the Appendix (Table A-4, Table A-5). Disagreements were solved through consensus.

Details zu IHE Checkliste

For the 'IHE RoB checklist', overall, RoB was assessed using a predefined point score (range: 0-20, Table 3-1): Higher scores indicate a low RoB, and lower scores indicate a high RoB. Detailed thresholds are presented in Table 3-2.

Table 3-1: Overall risk of bias point scores for risk of bias assessment of case series

Answers to specific questions of the IHE-20 checklist	Points
No	**0**
Partial	**0.5**
Unclear	**0.5**
Yes	**1**

Table 3-2: Cut-off criteria for the risk of bias assessment of overall risk of bias of case series

Criteria	Points
Low risk	**> 18**
Moderate risk	**14.5 to 18**
High risk	**≤ 14**

3.2.4 Synthesis

Evidenzsynthese mittels GRADE

Based on data extraction tables (see Appendix, Table A-2 and Table A-3), data on each selected (critical) outcome category were, if applicable, synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [28]. The research questions were answered in plain text format with reference to GRADE evidence tables (Table A-6).

4 Results: Clinical effectiveness and safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

entscheidungsrelevante Wirksamkeits-Endpunkte

In discussion with clinical experts, the following effectiveness outcomes were defined as most relevant to patients with unresectable liver cancer. Therefore, these outcomes were defined as *crucial* to derive a recommendation:

- Overall survival: defined as time of first M-PHP until death or censoring [4]
- Overall progression-free survival: defined as time of first M-PHP until progressive disease, death, or censoring [4]
- Hepatic progression-free survival: defined as time of first M-PHP until progressive disease, death, or censoring [4]
- Quality of life[33]: using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 (EORTC QLQC30 v3.0) at baseline, six weeks after the first and second M-PHP, and six months after the first M-PHP [4]

weitere wichtige Endpunkte

Further effectiveness outcomes were defined as *important*, but not crucial to derive a recommendation:

Messinstrumente

- Hepatic objective response: according to Response Evaluation Criteria In Solid Tumors (RECIST 1.1) [4]
- Objective response rate: according to Response Evaluation Criteria In Solid Tumors (RECIST 1.1) [4]

Survival endpoints were calculated from the time of the treatment randomisation to the event. Survival and response calculations were based on a blinded, outside independent image review committee (IRC). All treatment decisions were based on an investigator (INV) assessment of response. [29].

4.1.2 Outcomes safety

entscheidungsrelevanter Sicherheits-Endpunkt

The following safety outcome was defined – in discussion with clinical experts – as most relevant to patients with unresectable liver cancer. Therefore, this outcome was defined as *crucial* to derive a recommendation:

- Death

weitere wichtige Endpunkte

Further safety outcomes were defined as *important*, but not crucial to de-rive a recommendation:

Definition und Messinstrument

- Toxicity incl. bone marrow or haematological toxicity
- Procedure-related complications, incl. liver toxicity, febrile neutropenia, infection, haemorrhage, thromboembolic and cardiovascular events
- Discontinuation of therapy

[33] Not measured in the included RCT [29]

Safety outcomes such as serious adverse events occurring within 30 days after M-PHP procedure were defined as severe complications resulting in, e.g., death. Safety, toxicity, and serious adverse events were assessed and reported according to the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03)[34] [4, 7].

4.2 Included studies

4.2.1 Included studies effectiveness

Primary liver cancer

No studies regarding primary liver cancer could be identified.

Secondary liver cancer

Study and patient characteristics

1 RCT mit Crossover eingeschlossen

The evidence included in the effectiveness domain consists of one multicentre phase III RCT [29], where patients of the control group crossed over to the treatment arm if they had evidence of disease progression, identified by the literature search (Figure 3-1). The primary endpoint was hepatic progression-free survival with an intention-to-treat analysis [29].

USA

This RCT with an overall high RoB was conducted in the USA, sponsored by the Intramural Program of the National Cancer Institute, National Institutes of Health. There was a Cooperative Research and Development Agreement (CRADA) between Delcath Systems, Inc., and the Surgery Branch of the National Cancer Institute. The first generation of the CHEMOSAT® Delcath Systems was compared to the best alternative care, mainly systemic chemotherapy (n=24) and chemoembolisation (n=11) [29].

Filter erster Generation

sekundärer Leberkrebs von Augen- oder Hautmelanom

Patients (n=93; IG: n=44, median age 55, range 33-74; CG: n=49, median age 56, range 31-77) with unresectable ocular or cutaneous melanoma metastatic to the liver were recruited between 2006 and 2009. Co-morbidities were not reported. Considering only the patients receiving the intervention (M-PHP), a total of 70 patients were observed, i.e., patients randomised to the M-PHP group (n=42) *and* after crossover to the M-PHP group (n=28)[35] [29].

Einschlusskriterien

Inclusion criteria were biopsy-proven unresectable melanoma metastatic to the liver, Eastern Cooperative Oncology Group performance status of ≤2, serum bilirubin ≤2.0 mg/dl, platelet count >100,000, serum creatinine <1.5 mg/dl, and liver function tests <10 times the upper limit of normal [29].

Beobachtungszeitraum

All patients were imaged and followed while receiving active treatment at 6-week ± 2-week intervals. Patients entered the 'follow-up phase' when off active treatment. During this phase, they were evaluated for disease progression every eight weeks (for the remainder of the first year), every three months

[34] See https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (access date 26/01/2022)

[35] Intention-to-treat was used to analyse the outcomes were hepatic progression free survival, overall progression free survival, and overall survival [29].

(the second year), every four months (for the third year), every six months (for the fourth year), and yearly thereafter. The outcome survival was assessed every six months (for the first two years) and then yearly after that. No loss to follow-up was reported [29].

Study characteristics and results of included studies are displayed in Table A-2 and Table A-3 and the evidence profile in Table A-6.

4.2.2 Additional included studies safety

Primary liver cancer

No studies regarding primary liver cancer could be identified.

Secondary liver cancer

1 Fallserie (2 Publikationen), nur sekundärer Leberkrebs von Augenmelanom, Filter zweiter Generation

In the safety domain, the evidence consists of two prospective, single-arm, single-centre case series (phase II) [4, 7] from the Netherlands reporting on the same study. Delcath Systems Inc. sponsored the study as the Leiden University Medical Center received financial support and contributions. The second generation of the CHEMOSAT® Delcath Systems was used. Thirty-five patients (median age 59 years, range 41-71) with unresectable ocular melanoma metastases confined to the liver were recruited between 2014 and 2017. Inclusion criteria were histologically proven, unresectable ocular melanoma metastases confined to the liver. Follow-up was at a median of 19.1 months (range 5.6-69.5) with no loss to follow-up [4, 7].

Study characteristics and results of included studies are displayed in Table A-2 and Table A-3 and the evidence profile in Table A-6.

4.3 Results

Primary liver cancer

No evidence regarding primary liver cancer could be identified.

Secondary liver cancer

Survival and mortality[36]

Gesamtüberleben: kein statistisch signifikanter (s.s.) Unterschied der 2 Gruppen

The median *overall survival* was 10.6 months (95% CI 6.9-13.6 months) in the M-PHP group compared with 10.0 months (95% CI 6.0-13.1 months) in the control group receiving best alternative care. There was no statistically significant difference between the two randomised groups (p>0.05) [29].

Subgruppenanalyse

In a subgroup analysis of patients of the control group who crossed over and received M-PHP treatment (n=28, 57.1%), the median overall survival was 13.1 months (95% CI 10.0-20.3 months) [29].

[36] **D0001** – What is the expected beneficial effect of percutaneous hepatic perfusion on mortality?

allgemein-progressionsfreies Überleben: s.s. länger in M-PHP-Gruppe

The median *overall progression-free survival* in the M-PHP group was statistically significantly longer (5.4 months [95% CI 3.4-8.1 months]) than in the control group receiving best available care (1.6 months [95% CI 1.5-2.3 months]) with a p-value of p<0.0001 [29].

hepatisch-progressionsfreies Überleben: s.s. länger in M-PHP-Gruppe

Also, median *hepatic progression-free survival* was statistically significantly longer (p<0.0001) in the M-PHP group (7.0 months [95% CI 5.2-9.7 months]) compared to the best alternative care group (1.6 months [95% CI 1.5-2.9 months]) [29].

Morbidity incl. hepatic objective response (tumour response) and objective response rate[37]

hepatisch-objektive Ansprechrate: s.s. höher in M-PHP-Gruppe

A statistically significant improvement favouring the M-PHP group could be found when comparing hepatic objective response between the two groups (p<0.001). The *hepatic objective response* rate (all partial response) in the M-PHP group was 36.4% (n=16) with an additional *stable disease rate* of 52.3% (n=23) and *overall hepatic disease control rate* of 75% (n=33). The *hepatic objective response* rate (all partial response) was 2% (n=1) in the control group. Additionally, 40.8% (n=20) achieved *stable disease rate*, for an *overall hepatic disease control rate* of 42.9% (n=21) [29].

objektive Ansprechrate: s.s. höher in M-PHP-Gruppe

The *objective response rate* was statistically significantly higher in the M-PHP group (27.3%, n=13) compared to the control group (4.1%, n=2) with a p-value of p<0.01. The median duration of objective response was 6.3 months in the M-PHP group and 3.7 months in the control group [29].

Function

Funktion: keine Evidenz

None of the included studies assessed M-PHP's effects on patients' body functions[38] or activities of daily living[39].

Health-related quality of life and patient satisfaction

Lebensqualität: keine Evidenz

Neither changes in quality of life were assessed[40], nor if the use of M-PHP was worthwhile for the patients [29].[41]

Patient safety

Crossover-Patient*innen in RCT

According to the study protocol of the RCT, patients of the control group may cross over to the treatment arm if they had evidence of disease progression. Therefore, considering all patients receiving the treatment (M-PHP), a total of 70 patients were observed (i.e., patients randomised to the M-PHP group (n=42) *and* after crossover to M-PHP group (n=28) [29].

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[37] **D0005** – How does percutaneous heptic perfusion affect symptoms and findings (hepatic objective response, objective response rate) of the disease or health condition?

[38] **D0011** – What is the effect of M-PHP on patients' body functions?

[39] **D0016** – How does the use of M-PHP affect activities of daily living?

[40] **D0012** – What is the effect of M-PHP on generic health-related quality of life?; **D0013** – What is the effect of M-PHP on disease-specific quality of life?

[41] **D0017** – Was the use of M-PHP worthwhile?

Death[42]

4 Todesfälle (RCT)

In the RCT, 4.3% (n=4/93 patients) of adverse events that caused *death* were reported. Thereof, three deaths were attributed to M-PHP (bone marrow suppression n=2, progressive hepatic failure n=1), while a single death resulted from gastric perforation (1 study) [29].

keine Todesfälle (Fallserie)

No deaths were reported in the prospective, single-arm, single-centre case series (2 publications) [4, 7], resulting from the same study (1 study).

Procedure-related complications

90 % peri-prozessuale Ereignisse (Grad 3) (RCT)

In the RCT, *peri-procedural events*[43] (grade 3/4 events) were observed in 90% of the M-PHP group (n=63/70[44] patients). The following events were described: any treatment-emergent adverse event in 63 patients (90.0%), hemoglobin decreased in 42 patients (60.0%), platelet count decreased in 52 patients (74.3%), activated partial thromboplastin time prolonged in 18 patients (25.7%), aspartate transaminase increased in 14 patients (20.0%), blood albumin decreased in 26 patients (37.1%), blood bilirubin increased in seven patients (10.0%), blood calcium decreased in 16 patients (22.9%), international normalised ratio increased in 14 patients (20.0%), neutrophil count decreased in 3 patients (4.3%), and hepatic artery spasm occurred in 46 patients (67.0%). *Central nervous system-associated events* such as cerebral ischemia and facial paresis occurred in one patient (1.4%), respectively (1 study) [29].

91 % post-prozessuale Ereignisse (Grad 3) (RCT)

Post-procedural events[45] (grade 3/4 events) were observed in 91.4% of the M-PHP group (n=64/70 patients) in the RCT. The following events were mentioned: any treatment-emergent adverse event occurred in 64 patients (91.4%), haemoglobin decreased in 44 patients (62.9%), platelet count decreased in 56 patients (80.0%), aspartate transaminase increased in seven patients (10.0%), blood albumin decreased in 4 patients (5.7%), blood bilirubin increased in ten patients (14.3%), international normalised ratio increased in one patient (1.4%), febrile neutropenia occurred in 12 patients (17.1%), neutrophil count decreased in 60 patients (85.7%), and hepatic dysfunction occurred in ten patients (14.3%) (1 study) [29].

nur 1 Publikation von Fallserie hier beschrieben

Concerning the case series (1 study, 2 publications), the publication from 2019 [7] describes safety and toxicity outcomes in more detail than those published in 2020 [4]. This is because patient organisations and medical authorities requested an M-PHP's safety profile using the second generation filter to become publicly available at the earliest possible stage [4]. Therefore, the published results on safety [7] are presented in the following.

2 % schwerwiegende unerwünschte Ereignisse (Fallserie)

Serious adverse events occurred in 14 (2%) of 67 procedures in the observational study. Thereof, *a potentially life-threatening situation* occurred in one procedure (2%) (i.e., transient cardiac ischemia). *Prolonged hospital admission*[46] occurred in five procedures (8%) (i.e., post-procedural hypotension (asympto-

[42] C0008 – How safe is percutaneous hepatic perfusion in comparison to best alternative care?

[43] "Occurring from the date of the planned procedure until the earlier of 72 hours post-procedure or patient discharge from the hospital [29]".

[44] Including both randomised to M-PHP group (n=42) and after crossover to M-PHP group (n=28) [29].

[45] "Occurring between the end of the peri-procedural period until 30 days after dosing, or until the start of the next treatment cycle [29]."

[46] "4-5 days (instead of 3 days)" [7]

matic), peri-procedural difficulties with oxygenation, post-procedural ECG changes (asymptomatic), pulmonary emboli, and nausea/vomiting with mild hypokalemia, respectively one procedure (2%)). Readmission [47] occurred in eight procedures (12%), e.g., due to febrile neutropenia in two procedures (3%) (1 study) [7].

nicht-hämatologische/ -hepatische Komplikationen: in 87 % (alle Grade), 21 % (Grad 3) und 2 % (Grad 4) (Fallserie)

In the observational study, *non-hematologic and non-hepatic complications* were divided into all-grades events, grade 3 and grade 4 events and measured in a total of 67 procedures (serious adverse events from above are incorporated). All-grades events occurred in 58 (87%) of 67 procedures, grade 3 events in 14 (21%) of 67 procedures, and grade 4 events in one (2%) (i.e., sepsis with bacterial pharyngitis and retropharyngeal abscess) of 67 procedures. The most common all-grades events were post-procedural haemorrhage (n=11), generalised oedema and/or pleural effusion (n=8), fever (n=7), and nausea (n=7). The most common occurring grade 3 events were febrile neutropenia (n=3), post-procedural haemorrhage (n=2), and pulmonary emboli (n=2) (1 study) [7].

frühe und späte Ereignisse

Hematologic events, and the following hepatic events, in all technically successful procedures, are divided into early[48] and late[49] events.

hämatologische Ereignisse: z. B. Blutarmut (alle Grade), Lymphopenie (Grad 3), Neutropenie (Grad 4) (Fallserie)

Hematologic events were measured in total 62 procedures in the observational study. *All-grades hematologic events*[50] were mentioned such as anaemia (early: 62 procedures (100.0%); late: 61 procedures (98.4%)), thrombocytopenia (early: 58 procedures (93.5%) ; late: 45 procedures (72.6%)), leukopenia (early: 10 procedures (16.1%); late: 45 procedures (72.6%)), neutropenia (early: NR; late: 34 of 61 procedures (55.7%)), lymphocytopenia (early: 42 of 45 procedures (93.3%); late: 48 of 59 procedures (81.4%)). The following *grade 3 events* occurred: anaemia (early: 1 procudure (1.6%); late: five procedures (8.1%)), thrombocytopenia (early: 6 procedures (9.6%); late: 11 procedures (17.7%)), leukopenia (early: NR; late: 9 procedures (14.5%)), neutropenia (early: NR; late: 2 procedures (3.3%)), and lymphocytopenia (early: 17 procedures (37.8%); late: 23 procedures (39.0%)). *Grade 4 events* occurred such as thrombocytopenia (early: NR; late: 11 procedures (17.7%)), leukopenia (early: NR; late: 22 procedures (35.5%)), neutropenia (early: NR; late: 26 procedures (42.6%)), and lymphocytopenia (early: 5 procedures (11.1%); late: 13 procedures (22.0%)) (1 study) [7].

hepatische Ereignisse: erhöhte Aminotransferasen (Fallserie)

In the observational study, *hepatic events* were measured in 62 procedures. The following all-grades events were stated: increased alanine aminotransferase (early: 34 procedures (54.8%); late: 36 procedures (58.1%)), increased aspartate aminotransferase: early: 43 procedures (69.4%); late: 21 of 60 procedures (35.0%)), and increased bilirubin (early: 5 of 57 procedures (8.8%); late: 6 of 60 procedures (10.0%)). Grade 3 and 4 events did not occur. There was a statistically significant decrease ($p<0.001$) in haemoglobin and platelet levels and lymphocyte count during the early phase (1 study) [7].

[47] "Median hospital stay of 6 days, range 1-15" [7]

[48] "Early events (0–3 days)" [7]

[49] "Late events (4–30 days)" [7]

[50] All events of 'all grades' were also investigated for 'grade 3' and 'grade 4'. For reasons of clear presentation we did not report events which did not occur.

Toxicity incl. bone marrow or haematological toxicity

17 % Herztoxizität (RCT)

In the RCT, *peri-procedural events* such as end-organ toxicity were measured in 70[51] patients. Cardiac toxicity was reported in 12 patients (17.1%) and was mainly manifested by elevated troponin in six patients (8.6%) and sinus tachycardia in two patients (2.9%). *Post-procedural events* were related to the effects of bone marrow suppression (1 study) [29].

s.s. Aminotransferasen-Anstieg (Fallserie)

In the observational study, there were no grade 3 and 4 hepatic events, a statistically significant increase ($p<0.01$) of aminotransferases was observed, indicating some degree of hepatic toxicity (1 study) [7].

Discontinuation of therapy

Behandlungsabbrüche: 96 % (RCT) …

In the RCT, in 67 (95.8%) of 70 patients (including both randomised to PHP group and after crossover to PHP group), therapy was not continued. The reasons were: *Disease progression* occurred in 20 patients (28.6%), mainly due to extrahepatic progression (15 patients (21.4%)). In 24 patients (34.3%), *adverse events* occurred mainly due to decrease platelet count (12 patients (17.1%)). Furthermore, discontinuation of M-PHP therapy was stated due to the investigator's opinion (9 patients (12.9%)), completed four cycles of treatment and no clinical indication to continue (5 patients (7.1%)), completed six cycles of PHP therapy or equivalent of best alternative care (twelve 3-week cycles) in two patients (2.9%), and patient decision (1 patient (1.4%)). No loss to follow-up was reported (1 study) [29].

… und 8 % (Fallserie)

In the observational study, in five (7.5%) of 67 procedures, discontinuation of therapy was described mainly due to filter clotting (3 procedures) (1 study) [7].

[51] Including both randomised to M-PHP group (n=42) and after crossover to M-PHP group (n=28) [29].

5 Quality of evidence

moderates bis hohes Verzerrungsrisiko

RoB of the RCT [29] was assessed by the Cochrane Collaboration tool version 2 [30]. The overall high RoB arose from the randomisation process and from the lack of measurements of the outcomes. In the two observational studies [4, 7], RoB was moderate assessed by the IHE checklist [31]. Serious limitations were given due to the single-centre design, and patients entered the study at a different point in the disease. Two researchers (LG, VH) independently rated the RoB presented in Table A-4 and Table A-5.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE schema [28] for each crucial efficacy endpoint and all safety endpoints individually. Crucial efficacy outcomes and all safety outcomes were graded and rated by two independent researchers (LG, VH). In case of disagreement, a third researcher was involved in solving the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [28].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below (Table 5-1) and the evidence profile in Appendix Table A-6.

sehr niedrige bis moderate Qualität der Evidenz

The overall strength of evidence for the *efficacy* of PHP using the Hepatic CHEMOSAT® Delivery System compared to best alternative care was low (overall survival) to moderate (overall progression-free survival, hepatic progression-free survival). For the outcome quality of life, no evidence is available. The overall strength of evidence for *safety* was very low in all outcomes (death, procedure-related complications, bone marrow or haematological toxicity, and discontinuation of therapy).

Table 5-1: Summary of findings table of percutaneous hepatic perfusion (PHP) for patients with secondary liver cancer (Hepatic CHEMOSAT® Delivery System)

Outcome	Efficacy: Absolute effects (95% CI) Safety: n (%)		Number of participants (studies)	Quality
	Effect with melphalan percutaneous hepatic perfusion	Effect with best alternative care		
Efficacy (6 week ± 2-week intervals[52])				
Overall survival	10.6 months (95% CI 6.9-13.6 months)	10.0 months (95% CI 6.0-13.1 months)	93 (1 RCT)	Low
	p>0.05			
Overall progression-free survival	5.4 months (95% CI 3.4-8.1 months)	1.6 months (95% CI 1.5-2.3 months)	93 (1 RCT)	Moderate
	p<0.0001			
Hepatic progression-free survival	7.0 months (95% CI 5.2-9.7 months)	1.6 months (95% CI 1.5-2.9 months)	93 (1 RCT)	Moderate
	p<0.0001			
Quality of life	NA	NA	NA	NA
Safety (6-8 week intervals[52])				
Death	*RCT:* IG: 3/93 (3.2); CG: 1/93 (1.1)[53] *Observational study:* 0 (0)		128 (1 RCT, 1 case series)	Very low
Procedure-related complications	Peri: 63/70 pts (90) Post: 64/70 pts (91.4) Serious adverse events: 14/67 procedures (2)		128 (1 RCT, 1 case series)	Very low
Bone marrow or haematological toxicity	Peri: 12/70 pts (17.1)		128 (1 RCT, 1 case series)	Very low
Discontinuation of therapy	67/70 procedures (95.8) 5/67 procedures (7.5)		128 (1 RCT, 1 case series)	Very low

Abbreviations: CI – confidence interval. NA – not available/applicable. Pts – patients.

[52] While receiving active treatment.

[53] 3 deaths were attributed to M-PHP in patients randomised to M-PHP (i.e., bone marrow suppression n=2, progressive hepatic failure n=1); 1 death was due to gastric perforation.

6 Discussion

Primary liver cancer is rare, but one of the most lethal cancers worldwide with a dismal prognosis; metastases to the liver (secondary liver cancer) are more common [1]. Even if the primary tumour is successfully treated, up to 50% of patients eventually develop metastatic diseases with predominant liver involvement [4]. The medical device Hepatic CHEMOSAT® Delivery System is used to treat patients with surgically unresectable primary and secondary liver tumours [1]. For this systematic review, melphalan chemosaturation with percutaneous hepatic perfusion (M-PHP) is compared to best available care concerning efficacy and safety outcomes. M-PHP represents a repeatable and minimally invasive hepatic therapy technique where the liver is isolated from the systemic circulation [4, 5].

Leberkrebs: schlechte Prognose, in 50 % der Fälle Metastasen in Leber

M-PHP: minimal-invasiv und wiederholbar

Summary of evidence

This systematic review identified the best available evidence consisting of one multicentre RCT (phase III), including a crossover of the control group to M-PHP treatment [29]; and two prospective, single-arm, single-centre case series (phase II) [4, 7], reporting on the same study. In total, 128 patients were assessed with a median age range from 31 to 77 years. Generation 1 of the CHEMOSAT® Delcath Systems was used in the RCT [29] and generation 2 in the observational studies [4, 7], treating patients with unresectable ocular or cutaneous melanoma metastases confined to the liver (only secondary liver cancer). No loss to follow-up was reported in the three articles. Currently, no recommendation in guidelines is given regarding PHP in patients with liver cancer.

1 RCT und 1 Fallserie (2 Publikationen) eingeschlossen

nur sekundärer Leberkrebs untersucht

keine Empfehlung in Leitlinien

Clinical effectiveness and safety

Effectiveness

Evidence was found indicating that M-PHP compared to best available care may be more effective regarding overall and hepatic progression-free survival ($p<0.0001$, respectively), hepatic objective response ($p<0.001$), and objective response rate ($p<0.01$). No evidence concerning quality of life could be found, and overall survival did not statistically significantly improve ($p>0.05$) due to M-PHP compared to best available care [29].

M-PHP effektiver als bestmögliche Behandlung …

The failure demonstrating a benefit of M-PHP on *overall survival* in the RCT by Hughes et al. [29] may be due to the cross over: Patients of the control group crossed over to the treatment arm if they had evidence of disease progression. The high crossover of patients of the control group (57.1%) to the M-PHP treatment group may have confounded any possible overall survival advantage [14]. They crossed over with similar efficacy, and therefore, the study may not address the question of overall survival, and the comparison may not be appropriate [19, 29]. Furthermore, a substantial number of 40% of patients had extrahepatic metastases (metastases outside the liver), which might limit the liver-directed therapy's optimal effect. Therefore, it may be that no impact on overall survival could be noted [4].

… nicht jedoch hinsichtlich Gesamtüberleben

möglicherweise aufgrund Crossover, Krebs auch außerhalb Leber und bereits fortgeschrittene Erkrankung

ev. Ergebnissbeeinflussung durch Messinstrumente

In the included RCT, all treatment decisions were based on an investigator (INV) assessment of response, survival and response calculations were based on a blinded, outside independent image review committee (IRC) [29]. However, an independent review committee (IRC) may influence the assessment of overall survival, overall and hepatic progression-free survival [32].

1 Meta-Analyse im Vergleich mit teilweise abweichenden Ergebnissen

Comparing our results with systematic reviews and meta-analyses, only one study from 2021 could be identified. This identified meta-analysis compared M-PHP and IHP to treat uveal melanoma liver metastases [18]. Nine articles (eight studies: six retrospective cohorts, one phase II clinical trial, and one combined reporting of phase I + phase II clinical trial) were included in the analysis. Median *overall survival* in the M-PHP treatment group was 17.3 months (10.6 months in our results) compared to 17.1 months for IHP. Median *progression-free survival* was 9.6 months for PHP (5.4 months in our results) and 7.2 months for IHP. Median *hepatic progression-free survival* was 9.5 months for PHP (7.0 months in our results) and ten months for IHP [18]. In contrast, some of these results deviate from ours, which may be due to the open study design of the meta-analysis, including also retrospective studies.

ev. aufgrund offenen Studiendesigns

1 Meta-Analyse untersuchte *verschiedenste* Behandlungsmodatlitäten mit …

Another meta-analysis investigated overall survival after treatment in patients with metastatic uveal melanoma in a systematic review and meta-analysis using a range of different treatment modalities. 78 articles with 2,494 patients were included in the analysis. Used treatment modalities were mainly surgery (n=500), TACE (n=484), hepatic intra-arterial chemotherapy (n=355), checkpoint inhibitor (n=318), conventional chemotherapy (n=272 patients), IHP (n=147), and chemoimmunotherapy with interferon and interleukin (n=107) [33]. Unfortunately, PHP was not assessed.

… sehr geringem Gesamtüberleben

The median overall survival across all treatment modalities was only 1.07 years (range: 0.59-2.50 years). After IHP, a pooled overall survival of only 1.3 years was reported. The results of this meta-analysis suggest no clinically significant difference in overall survival by the treatment modality [33]. Comparing these results to ours (overall survival in the M-PHP group: 10.6 months), an immense difference can be found in favour of M-PHP. But also for IHP, our results for overall survival was much longer with ten months, compared to the meta-analysis.

Safety

4 Todesfälle, 90 % prozessuale Ereignisse

Four (4.3%) *deaths* in 93 investigated patients were reported in the RCT [29], whereof three deaths were attributed to M-PHP in patients randomised to M-PHP. No deaths occurred in the observational studies [4, 7]. *Procedure-related complications* were observed in the majority of patients (peri-procedure: 63 (90%) of 70 pts; post-procedure: 64 (91.4%) of 70 patients) [29]. *Serious adverse events* were reported in 14 (2%) of 67 procedures [4, 7] and *end-organ toxicity* in 12 (17.1%) of 70 patients [29]. 67 (95.8%) of 70 patients [29] *discontinued* M-PHP therapy, and five (7.5%) of 67 procedures [4, 7] were discontinued. This discrepancy in discontinuation of M-PHP therapy must be evaluated in future studies.

Diskrepanz in Behandlungsabbrüchen

Filter-Generation 1 vs. 2

The included RCT [29] used the generation 1 filter, and the observational studies [4, 7] already used the generation 2 filter. Therefore, future studies using the generation 2 filter may improve haematological toxicity values. Consequently, there is a need for updated data concerning the efficacy of M-PHP for treating primary or secondary liver cancer and supplement data regarding safety [5].

NICE: Filter und unzureichende Abdichtung beeinflussen Toxizität

The committee of the NICE guidance [19] stated that the procedure's toxicity is principally related to how efficiently melphalan is removed and prevented from entering the patient's systemic circulation. The technology has changed over time, so the generation 2 filter may be associated with less haematological toxicity. Furthermore, systemic toxicity may be attributed to other factors and not only to incomplete filtration. Also, chemotherapeutics reaching the systemic circulation through venous collaterals or insufficient sealing of the balloons may lead to systemic toxicity in the body [7]. However, our results support the reasoning of NICE, stating that the evidence of safety shows serious, well-recognised complications.

Sicherheitsendpunkte nicht alle vergleichbar

It must be stated that the included studies selectively described the grade of safety events by the Common Terminology Criteria of Adverse Events (CTCAE), i.e., all events, grade 3 and 4 safety events. Therefore, it is hard to compare these events. Furthermore, patients *or* procedures are reported that cannot be compared eighter.

Meta-Analyse: Endpunkte nicht vergleichbar

The identified meta-analysis reported a complication rate and 30-day mortality rate of 23.8% and 1.8% for PHP and 39.1% and 5.5% for IHP. Unfortunately, these outcomes cannot be compared to ours. The authors of the meta-analysis concluded that patients of the M-PHP had significantly less risk for complications and mortality compared to IHP [18].

Internal and external validity

sehr niedrige bis moderate Qualität der Evidenz

Overall, the strength of evidence for clinical *effectiveness* outcomes was low (overall survival) to moderate (overall and hepatic progression-free survival), mainly due to a high RoB of the RCT [29]. Regarding the *safety* of M-PHP treatment, the quality of evidence was very low in all (crucial and important) outcomes. Evidence was downgraded due to the high RoB, inconsistency, indirectness, and imprecision [4, 7, 29].

moderates bis hohes Verzerrungsrisiko

Across the three included articles, RoB was moderate (observational study) [4, 7] to high (RCT) [29]. Several limitations of the best available evidence need to be considered: High RoB [29] arises from a lack of information regarding the randomisation process and from a lack of measurements of the outcomes. Moderate RoB arises from the single-centre design and patients entering the study at a different point in the disease [4, 7].

kleine Studienpopulation

The small number of included participants across the studies (35-93 patients) could have influenced the occurrence of safety events. However, this can be explained by the rarity of the disease.

Limitations

nur sekundärer Leberkrebs

Studienausschluss

This systematic review results should be interpreted in light of its limitations. Only one RCT and further two observational studies could be identified investigating secondary liver cancer, but not primary liver cancer. Retrospective studies – and for safety also prospective case series (if not $n \geq 10$) – were excluded, and, therefore, we possibly missed data. However, retrospective studies are more prone to internal validity concerns. This occurs due to limited information on confounding variables and general disability in controlling these variables adequately and convincingly compared to high-quality RCTs. Therefore, the inclusion of retrospective studies would not have changed the conclusion regarding the efficacy and safety of M-PHP.

Bedenken bezüglich Gültigkeit

Furthermore, filters of generations 1 and 2 were used in the included studies, which also may affect the generalisability derived from safety results. Applicability concerns are described in the applicability table (see Table A-7).

Ongoing studies

1 RCT mit 295 Patient*innen

voraussichtliche Fertigstellung in 2023

The search for ongoing studies revealed that there is currently one ongoing RCT (NCT03086993; EudraCT Number: 2016-003812-10) in the USA sponsored by Delcath Systems Inc. This trial compares efficacy, safety and pharmacokinetics of M-PHP given sequentially following cisplatin/gemcitabine versus cisplatin/gemcitabine (standard of care) in patients with intrahepatic cholangiocarcinoma. The planned number of subjects to be included in the whole clinical trial is 295 patients. The measured primary outcome is overall survival. For the injection of melphalan, the Delcath hepatic delivery system is used, and the estimated completion date is May 2023 (see Table A-8).

Conclusion

Evidenz unzureichend

Effektivität teilweise gegeben, jedoch schwerwiegende Komplikationen

The given evidence is insufficient and with limited internal and external validity to show clinical benefits of M-PHP in patients with secondary liver cancer compared to best available care. The only RCT demonstrated that M-PHP is more effective in overall and hepatic progression-free survival than best available care. Furthermore, overall survival did not statistically significantly improve due to M-PHP. However, serious, well-recognised complications regarding safety outcomes were shown. Due to the overall very low strength of evidence and high RoB of the RCT, no definitive conclusions on the comparative effectiveness of M-PHP can be drawn.

verschiedene Filter-Generationen

Furthermore, different generations of filters were used, which may affect the applicability and generalisability derived from safety results. Therefore, no conclusion can be given that M-PHP is as safe as best available care.

hoch-qualitative RCTs notwendig

Further results from well-designed RCTs are lacking. In light of the available evidence, results of ongoing studies are to be awaited to shed more light on the comparative evidence of M-PHP versus best available care. Future research should focus on more high-quality RCTs with comprehensive safety reporting.

7 Recommendation

In Table 7-1, the scheme for recommendations is displayed, and the according choice is highlighted.

Table 7-1: Evidence-based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

The current evidence is insufficient to prove that chemosaturation with percutaneous hepatic perfusion to be used in patients with unresectable secondary liver cancer is more effective than and as safe as best available care. The quality of evidence is very low; therefore, the evidence indicates that the inclusion of percutaneous hepatic perfusion for secondary liver cancer in the catalogue of benefits can not be supported at this time.

Evidenz unzureichend:

sehr niedrige bis moderate Qualität der Evidenz

New study results will potentially influence the effect estimate considerably. A large RCT (>200 patients) with patient-relevant primary outcomes is ongoing (NCT03086993). Therefore, a re-evaluation is recommended in 2024.

Neubewertung 2024

8 References

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Appendix

Critical appraisal of the NICE guidance

Table A-1: Critical appraisal of the systematic review (NICE guidance [19])

A Measurement Tool to Assess Systematic Reviews (AMSTAR) tool	NICE guidance [19]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review, and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes
5. Did the review authors perform study selection in duplicate?	No information provided
6. Did the review authors perform data extraction in duplicate?	No information provided
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	NA
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	NA
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the results of the review?	Partial Yes
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
Overall Confidence	**Low**

Reasoning: *One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest*

Abbreviations: *NA – not available.*

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-2: Percutaneous hepatic perfusion (PHP) for patients with secondary liver cancer: Results from randomised controlled trials (n=1)

Author, year	**Hughes, 2016 [29]**
Country	USA
Sponsor	Intramural Program of the National Cancer Institute, National Institutes of Health; Cooperative Research and Development Agreement (CRADA) between Delcath Systems, Inc., and the Surgery Branch of the National Cancer Institute
Intervention/Product	CHEMOSAT® Delcath Systems
Generation 1 or 2 of Delcath system	1
Recruitment period	2006-2009
Comparator	Best alternative care[54]
Study design	Multicentre RCT (phase III) including a crossover of the control group to M-PHP treatment
Number of pts	93 (44 vs 49) Total PHP patients (n=70): Including both randomised to M-PHP group (n=42) and after crossover to M-PHP group (n=28)
Indication	Patients with unresectable ocular or cutaneous melanoma metastatic to the liver
Inclusion criteria	■ Biopsy proven, unresectable melanoma metastatic to the liver ■ Eastern Cooperative Oncology Group performance status of ≤2 ■ Serum bilirubin ≤2.0 mg/dl ■ Platelet count >100,000 ■ Serum creatinine <1.5 mg/dl ■ Liver function tests <10 times the upper limit of normal
Age of patients, yrs, median (range)	IG: 55.0 (33-74); CG: 56.0 (31-77)
Follow-up	■ While receiving active treatment: 6 week ± 2-week intervals ■ When off active treatment (='follow-up phase'): 8 weeks (1. year), 3 months (2. year), 4 months (3. year), 6 months (4. Year), yearly thereafter ■ Survival: 6 months (1. and 2. year), yearly thereafter
Loss to follow-up, n (%)	0 (0)[55]
Overall survival Months; median (95% CI); p-value	Before crossover: IG: 10.6 months (95% CI 6.9-13.6 months); CG: 10.0 months (95% CI 6.0-13.1 months); p>0.05 Subgroup analysis: 13.1 months (95% CI 10.0-20.3 months) in patients of the CG who crossed over and received M-PHP treatment (n=28, 57.1%)
Quality of life	NA
Overall progression-free survival Months; median (95% CI); p-value	Before crossover: IG: 5.4 months (95% CI 3.4-8.1 months); CG: 1.6 months (95% CI 1.5-2.3 months); **p<0.0001**
Hepatic progression-free survival Months; median (95% CI); p-value	Before crossover: IG: 7.0 months (95% CI 5.2-9.7 months); CG: 1.6 months (95% CI 1.5-2.9 months); **p<0.0001**

[54] Systemic chemotherapy (n=24), chemoembolisation (n=11), radioembolisation (n=3), combination systemic chemotherapy and embolisation (n=1), surgery (n=1), supportive care (n=9)

[55] This means randomised to M-PHP group (n=42), after crossover to M-PHP group (n=28), and total M-PHP patients (n=70).

Author, year	Hughes, 2016 [29]
Hepatic objective response, n (%)	Before crossover: IG: ■ hepatic objective response (all partial response): 16 (36.4) ■ stable disease rate: 23 (52.3) ■ overall hepatic disease control rate: 33 (75.0) CG: ■ hepatic objective response (all partial response): 1 (2.0) ■ stable disease rate: 20 (40.8) ■ overall hepatic disease control rate: 21 (42.9) hepatic objective response (IG vs CG): **p<0.001**
Objective response rate, n (%)	Before crossover: IG: 13 (27.3); CG: 2 (4.1) **p<0.01** Median duration of objective response: IG: 6.3 months; CG: 3.7 months
Procedure-related complications incl. liver toxicity, febrile neutropenia, infection, haemorrhage, thromboembolic and cardiovascular events, n (%)	***Peri-procedural events***[56] ***(grade 3/4 events):*** observed in 90% of the IG (n=63/70[57] pts) ■ Any treatment-emergent adverse event: 63 (90.0) ■ Hemoglobin decreased: 42 (60.0) ■ Platelet count decreased: 52 (74.3) ■ Activated partial thromboplastin time prolonged: 18 (25.7) ■ Aspartate transaminase increased: 14 (20.0) ■ Blood albumin decreased: 26 (37.1) ■ Blood bilirubin increased: 7 (10.0) ■ Blood calcium decreased: 16 (22.9) ■ International normalised ratio increased: 14 (20.0) ■ Febrile neutropenia: NA ■ Neutrophil count decreased: 3 (4.3) ■ Hepatic artery spasm: 46 (67.0) **Central nervous system-associated events:** ■ cerebral ischemia 1 (1.4) ■ facial paresis 1 (1.4) ***Post-procedural events***[58] ***(grade 3/4 events):*** Observed in 91.4% of the IG (n=64/70 pts) ■ Any treatment-emergent adverse event: 64 (91.4) ■ Haemoglobin decreased: 44 (62.9) ■ Platelet count decreased: 56 (80.0) ■ Activated partial thromboplastin time prolonged: NA ■ Aspartate transaminase increased: 7 (10.0) ■ Blood albumin decreased: 4 (5.7) ■ Blood bilirubin increased: 10 (14.3) ■ Blood calcium decreased: NA ■ International normalised ratio increased: 1 (1.4) ■ Febrile neutropenia: 12 (17.1) ■ Neutrophil count decreased: 60 (85.7) ■ Hepatic disfunction 10 (14.3)

[56] "Occurring from the date of the planned procedure until the earlier of 72 hours post-procedure or patient discharge from the hospital."

[57] Including both randomised to M-PHP group (n=42) and after crossover to M-PHP group (n=28).

[58] "Occurring between the end of the peri-procedural period until 30 days after dosing, or until the start of the next treatment cycle."

Author, year	Hughes, 2016 [29]
Toxicity incl. bone marrow or haematological toxicity, n (%)	***Peri-procedural events (measured in total 70[57] patients):*** **End-organ toxicity:** Cardiac toxicity (12/70 pts (17.1)) was manifested by elevated ■ troponin 6 (8.6) ■ sinus tachycardia 2 (2.9) ■ myocardial infarction 1 (1.4) ■ atrial fibrillation 1 (1.4) ■ pericardial effusion 1 (1.4) ■ ventricular tachycardia 1 (1.4) ■ renal toxicity 0 (0) **Post-procedural events:** were related to effects of bone marrow suppression (no values reported)
Discontinuation of therapy, n (%)	Discontinuation in 67 (95.8) of 70[59] pts **Reasons:** Disease progression: 20 (28.6) ■ Hepatic progression: 5 (7.1) ■ Extrahepatic progression: 15 (21.4) Adverse events: 24 (34.3) ■ Platelet count decreased: 12 (17.1) ■ Neutrophil count decreased: 5 (7.1) ■ Blood bilirubin increased: 4 (5.7) Patient decision: 1 (1.4) Investigator's opinion: 9 (12.9) Lost to follow-up: 0 (0) Completed four cycles of therapy and no clinical indication to continue: 5 (7.1) Completed six cycles of PHP therapy or equivalent of best alternative care (twelve 3-week cycles): 2 (2.9) Other: 6 (8.6)
Death, n (%)	IG: 3/93 (3.2)[60]; CG: 1/93 (1.1)

Abbreviations: CG – control group, CI – confidence interval, IG – intervention group, NA – not available, NR – not reported, PHP – percutaneous hepatic perfusion, pts – patients, RCT – randomised controlled trial, USA – United States of America, yrs – years.

[59] Including both randomised to M-PHP group (n=42) and after crossover to M-PHP group (n=28). Deaths are not incorporated and presented separated.

[60] 3 deaths were attributed to M-PHP in patients randomised to M-PHP (i.e., bone marrow suppression n=2, progressive hepatic failure n=1); 1 death was due to gastric perforation

Table A-3: Percutaneous hepatic perfusion (PHP) for patients with secondary liver cancer: Results from prospective case series (1 study, 2 publications)

Author, year	**Meijer, 2019 [7]**	**Meijer, 2020 [4]**
Country	The Netherlands	
Sponsor	The Leiden University Medical Center received financial support and in kind contributions from Delcath Systems Inc.[61]	
Intervention/Product	CHEMOSAT® Delcath Systems	
Generation 1 or 2 of Delcath system	2	
Recruitment period	2014-2017	
Comparator	NA	
Study design	Prospective, single-arm, single-centre case series (phase II)	
Number of pts	35	
Indication	Patients with unresectable ocular melanoma metastases confined to the liver	
Inclusion criteria	Histologically proven, unresectable ocular melanoma metastases confined to the liver	
Age of patients, yrs, median (range)	59 (41[62]-71)	
Follow-up	Median 19.1 months (range 5.6-69.5)	
Loss to follow-up, n (%)	0 (0)	
Overall survival Months; median (95% CI); p-value	NA	NA
Quality of life	NA	NA
Overall progression-free survival Months; median (95% CI); p-value	NA	NA
Hepatic progression-free survival Months; median (95% CI); p-value	NA	NA
Hepatic objective response, n (%)	NA	NA
Objective response rate, n (%)	NA	NA
Procedure-related complications incl. liver toxicity, febrile neutropenia, infection, haemorrhage, thromboembolic and cardio-vascular events n (%)	***Serious adverse events: 14 (2) of 67 procedures:*** **Potential life-threatening situation during procedure: 1 (2):** ■ Transient cardiac ischemia: 1 (2) procedure **Prolonged hospital admission[63]: 5 (8):** ■ Post-procedural hypotension (asymptomatic): 1 (2) ■ Peri-procedural difficulties with oxygenation: 1 (2) ■ Post-procedural ECG changes (asymptomatic): 1 (2)	***Serious adverse events (n=14/67 procedures):***[64] Prolonged hospital admission[63] (n=5) Readmissions[65] (n=8) **Grade 3/4 hematologic events:** Leukopenia 75.6% Lymphocytopenia 84.8% **Grade 3 non-hematologic events (n=14):** including peri-procedural transient cardiac ischemia (n=1)

[61] "The authors declare that Delcath Systems Inc. had no involvement in any part of the study and that they have no conflict of interest."

[62] In [7], a range of 42-71 is stated (instead of 41-71 as in [4]).

[63] 4-5 days (instead of 3 days)

[64] "A more detailed description of safety and toxicity has been reported previously [7] as medical authorities and patient organisations requested for the safety profile of M-PHP using the GEN 2 filter to become publicly available at the earliest possible stage." [4]

Author, year	Meijer, 2019 [7]	Meijer, 2020 [4]
Procedure-related complications incl. liver toxicity, febrile neutropenia, infection, haemorrhage, thromboembolic and cardio-vascular events n (%) *(continuation)*	■ Pulmonary emboli: 1 (2) ■ Nausea/vomiting with mild hypokalemia: 1 (2) **Readmission[65]: 8 (12):** ■ Sepsis with bacterial pharyngitis and retropharyngeal abscess: 1 (2) ■ Pulmonary emboli: 1 (2) ■ Vaginal haemorrhage with grade 2 anaemia: 1 (2) ■ Febrile neutropenia: 2 (3) ■ Febrile neutropenia with mucositis/esophagitis: 1 (2) ■ Prostatitis: 1 (2) ■ Abdominal pain (unknown cause): 1 (2) ***Non-hematologic and non-hepatic complications (procedures n=67; serious adverse events from above are incorporated):*** All grades: total 58 (87) of 67 procedures Grade 3: total 14 (21) of 67 procedures Grade 4: total 1 (2) of 67 procedures **All grades[66] (n=58/67 procedures):** Post-procedural hemorrhage: 11; Generalised edema and/or pleural effusion: 8; Fever: 7; Nausea: 7; Abdominal pain: 4; Alopecia: 3; Febrile neutropenia: 3; Diarrhea: 2; Pulmonary emboli: 2; Sepsis with bacterial pharyngitis and retropharyngeal abscess: 1; Cardiac ischemia during procedure: 1; Post-procedural hypotension: 1; Post-procedural ECG changes: 1; Bladder infection: 1; Cystitis, non-infective: 1; Prostatitis: 1; Peri-procedural difficulties with oxygenation: 1; Upper respiratory infection: 1; Vulva infection: 1; Hyperglycemia: 1 **Grade 3 (n=14/67 procedures):** Febrile neutropenia: 3; Post-procedural hemorrhage: 2; Pulmonary emboli: 2; Nausea: 1; Abdominal pain: 1; Cardiac ischemia during procedure: 1; Post-procedural hypotension: 1; Post-procedural ECG changes: 1; Prostatitis: 1; Peri-procedural difficulties with oxygenation: 1 **Grade 4 (n=1/67 procedures):** Sepsis with bacterial pharyngitis and retropharyngeal abscess: 1 ***Hematologic events (procedures n=62):*** **All grades[66]:** ■ Anaemia: early[67]: 62 (100.0); late[68]: 61 (98.4) ■ Thrombocytopenia: early: 58 (93.5) ; late: 45 (72.6) ■ Leukopenia: early: 10 (16.1); late: 45 (72.6) ■ Neutropenia: early: NR; late: 34 (55.7)[69]	**Grade 4 non-hematologic event (n=1)** Sepsis with bacterial pharyngitis and retropharyngeal abscess formation

[65] Median hospital stay of 6 days, range 1-15

[66] All events of 'all grades' were also investigated for 'grade 3' and 'grade 4'. For reasons of clear presentation we did not report events which did not occur.

[67] Early events (0–3 days)

[68] Late events (4–30 days)

[69] In 61 procedures

Author, year	Meijer, 2019 [7]	Meijer, 2020 [4]
Procedure-related complications incl. liver toxicity, febrile neutropenia, infection, haemorrhage, thromboembolic and cardio-vascular events n (%) *(continuation)*	■ Lymphocytopenia: early: 42 (93.3)[70]; late: 48 (81.4)[71] **Grade 3:** ■ Anaemia: early: 1 (1.6); late: 5 (8.1) ■ Thrombocytopenia: early: 6 (9.6); late: 11 (17.7) ■ Leukopenia: early: NR; late: 9 (14.5) ■ Neutropenia: early: NR; late: 2 (3.3) ■ Lymphocytopenia: early: 17 (37.8); late: 23 (39.0) **Grade 4:** ■ Thrombocytopenia: early: NR; late: 11 (17.7) ■ Leukopenia: early: NR; late: 22 (35.5) ■ Neutropenia: early: NR; late: 26 (42.6) ■ Lymphocytopenia: early: 5 (11.1); late: 13 (22.0) ***Hepatic events (procedures n=62):*** **All grades[66]:** ■ Alanine aminotransferase increased: early: 34 (54.8); late: 36 (58.1) ■ Aspartate aminotransferase increased: early: 43 (69.4); late: 21 (35.0)[72] ■ Bilirubin increased: early: 5 (8.8)[73]; late: 6 (10.0)[74] ■ Significant decrease in haemoglobin and platelet levels, and lymphocyte count during the early phase[75] **p<0.001**	
Toxicity incl. bone marrow or haematological toxicity, n (%)	Increase of aminotransferases indicated some degree of hepatic toxicity **p<0.01**	NR
Discontinuation of therapy n (%)	n=5/67 procedures (7.5): ■ filter clotting (n=3) ■ insufficient sealing of the cranial balloon at its atriocaval junction (n=1) ■ transient cardiac ischemia (n=1) In one patient with heparin-induced thrombocytopenia, filter clotting occurred twice despite using argatroban as alternative anticoagulant during 2. procedure	NR
Death, n (%)	0 (0)	0 (0)

Abbreviations: CG – control group, CI – confidence interval, IG – intervention group, NA – not available, NR – not reported, PHP – percutaneous hepatic perfusion, pts – patients, RCT – randomised controlled trial, USA – United States of America. yrs – years.

[70] In 45 procedures

[71] In 59 procedures

[72] In 60 procedures

[73] In 57 procedures

[74] In 60 procedures

[75] 0-3 days

Risk of bias tables and GRADE evidence profile

Table A-4: Risk of bias – study level (randomised studies), Cochrane Collaboration tool [30]

Trial	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Hughes, 2016 [29]	High[76]	Some concern[77]	Low[78]	High[79]	Low[80]	High[81]

Table A-5: Risk of bias – study level (case series), IHE checklist [31]

Study reference/ID	Meijer, 2019 [7]	Meijer, 2020 [4]
Study objective		
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes[82]	Yes[83]
Study design		
2. Was the study conducted prospectively?	Yes[84]	Yes[84]
3. Were the cases collected in more than one centre?	No[85]	No[85]
4. Were patients recruited consecutively?	Unclear[86]	Unclear[86]

[76] No information concerning the randomisation process could be found.

[77] No information about deviations that arose from the experimental context.

[78] Loss to follow-up or dropouts reported. Data available for (nearly) all participants.

[79] Study objectives and outcomes are described, but methods of measuring the outcome were not described at all.

[80] All outcomes described in the methods are also in the results. Study protocol available.

[81] The trial is judged to be at high risk of bias in at least one domain for this result.

[82] The hypothesis/aim/objective of the study was clearly reported (includes patients, intervention and outcome).

[83] The hypothesis/aim/objective of the study was clearly reported.

[84] It was clearly stated that the study was conducted prospectively.

[85] Cases were collected from one centre.

[86] No information was provided about the method used to recruit patients in the study.

Study reference/ID	Meijer, 2019 [7]	Meijer, 2020 [4]
Study population		
5. Were the characteristics of the patients included in the study described?	Yes[87]	Yes[87]
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes[88]	Yes[88]
7. Did patients enter the study at a similar point in the disease?	No[89]	No[89]
Intervention and co-intervention		
8. Was the intervention of interest clearly described?	Yes[90]	Yes[90]
9. Were additional interventions (co-interventions) clearly described?	Yes[91]	Yes[92]
Outcome measures		
10. Were relevant outcome measures established a priori?	Yes[93]	Yes[93]
11. Were outcome assessors blinded to the intervention that patients received?	Unclear[94]	Unclear[94]
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes[95]	Yes[95]
13. Were the relevant outcome measures made before and after the intervention?	Yes[96]	Yes[97]
Statistical Analysis		
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes[98]	Yes[98]

[87] All of the most relevant characteristics of the patients were reported.

[88] Both inclusion and exclusion criteria were reported.

[89] There was a wide range in the severity of the disease/condition and co-morbidities/complications in patients at baseline.

[90] All of the most relevant characteristics of the intervention were reported.

[91] Patients received routinely a subcutaneous injection of granulocyte colony stimulation factor within 72 h after each M-PHP.

[92] "Patients routinely received a subcutaneous injection of granulocyte-colony stimulating factor (pegfilgrastim 6 mg)" within 72 h after each M-PHP.

[93] All relevant outcome measures were stated in the methods section.

[94] The study did not report whether the outcome assessors were aware of the intervention.

[95] All relevant outcomes were measured with appropriate methods.

[96] The outcome measures were made pre and post-intervention. "Post-treatment laboratory test results were compared to pre-treatment results."

[97] The outcome measures were made pre and post-intervention.

[98] The statistical tests were used appropriately.

Study reference/ID	Meijer, 2019 [7]	Meijer, 2020 [4]
Results and Conclusions		
15. Was follow-up long enough for important events and outcomes to occur?	Yes[99]	Yes[99]
16. Were losses to follow-up reported?	Yes[100]	Yes[101]
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Partial[102]	Partial[102]
18. Were the adverse events reported?	Yes[103]	Yes[103]
19. Were the conclusions of the study supported by results?	Yes[104]	Yes[104]
Competing interests and sources of support		
20. Were both competing interests and sources of support for the study reported?	Yes[105]	Yes[105]
Overall Risk of bias	**16.5 (moderate risk)**	**16.5 (moderate risk)**

[99] It was clear from the information provided that the follow-up period was long enough for the majority (at least 80%) of patients, to allow for important events and outcomes (for example, changes in clinical status, adverse events) to occur.

[100] It is stated that „All patients were included in the analysis."

[101] "There was no loss to follow-up."

[102] The estimates of the random variability were reported for some, but not all of the relevant outcomes.

[103] The undesirable or unwanted events during the study period or within a pre-specified time period were reported.

[104] The conclusions of the study were supported by the evidence presented in the results and discussion sections.

[105] Both competing interests and sources of support (financial or other) received for the study were reported.

Table A-6: Evidence profile: efficacy and safety of the Hepatic CHEMOSAT® Delivery System in patients with secondary liver cancer [28]

Quality assessment							Summary of findings			
							Number of patients		Effect	Quality
Number of articles	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melphalan Percutaneous hepatic perfusion	Best alternative care	Absolute (95% CI) or n (%)	
Efficacy: Overall survival (followed and imaged at 6 week ± 2-week intervals)										
1	Randomised controlled trial	Very serious[a]	Not serious	Not serious	Not serious	Publication bias (undetected) Large effect (no) Plausible confounding (no) Dose response gradient (no)	44	49	IG: 10.6 months (95% CI 6.9-13.6 months); CG: 10.0 months (95% CI 6.0-13.1 months); p>0.05	Low[106]
Efficacy: Overall progression-free survival (followed and imaged at 6 week ± 2-week intervals)										
1	Randomised controlled trial	Very serious[a]	Not serious	Not serious	Not serious	Publication bias (undetected) Large effect (yes[107]) Plausible confounding (no) Dose response gradient (no)	44	49	IG: 5.4 months (95% CI 3.4-8.1 months); CG: 1.6 months (95% CI 1.5-2.3 months); **p<0.0001**	Moderate[108]
Efficacy: Hepatic progression-free survival (followed and imaged at 6 week ± 2-week intervals)										
1	Randomised controlled trial	Very serious[a]	Not serious	Not serious	Not serious	Publication bias (undetected) Large effect (yes[107]) Plausible confounding (no) Dose response gradient (no)	44	49	IG: 7.0 months (95% CI 5.2-9.7 months); CG: 1.6 months (95% CI 1.5-2.9 months); **p<0.0001**	Moderate[108]
Efficacy: Quality of life (followed and imaged at 6 week ± 2-week intervals)										
1	Randomised controlled trial	NA	NA	NA	NA	NA	44	49	NA	NA
Safety: Death (6-8 week interval)										
3	Randomised controlled trial (n=1)	Very serious[b]	Not serious	Serious[109]	Very serious[110]	Publication bias (undetected) Large effect (no) Plausible confounding (no) Dose response gradient (no)	44	49	*RCT:* IG: 3/93 (3.2); CG: 1/93 (1.1)[111] *Observational study:* 0 (0)	Very low[112]
	Prospective, single-centre, single-arm observational study (n=2)						35		n=0 (0%)	

[106] High risk of bias (-2).

[107] Hazard Ratio <1: means that the risk of survival is bigger for the intervention (M-PHP) group.

[108] High risk of bias (-2), large effect (+1).

[109] No direct (i.e., head-to-head) comparisons between two interventions.

[110] Only 93 (RCT) and 35 (observational study) included, and no confidence intervals stated.

[111] 3 deaths were attributed to M-PHP in patients randomised to M-PHP (i.e., bone marrow suppression n=2, progressive hepatic failure n=1); 1 death was due to gastric perforation.

[112] High risk of bias (-2), indirectness (-1), imprecision (-2).

Quality assessment							Summary of findings			
							Number of patients		Effect	Quality
Number of articles	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melphalan Percutaneous hepatic perfusion	Best alternative care	Absolute (95% CI) or n (%)	
Safety: Procedure-related complications (6-8 week interval)										
3	Randomised controlled trial (n=1)	Very serious[b]	Very Serious[113]	Serious[109]	Very serious[110]	Publication bias (undetected) Large effect (no) Plausible confounding (no) Dose response gradient (no)	44	49	*Peri-procedural events* (grade 3/4 events): in 90% of the IG (n=63/70 pts) *Post-procedural events* (grade 3/4 events): in 91.4% of the IG (n=64/70 pts)	Very low[114]
	Prospective, single-centre, single-arm observational study (n=2)						35		Serious adverse events: 14/67 (2) Non-hematologic/-hepatic events[115]: 14/67 (21) procedures (grade 3), 1/67 (2) procedures (grade 4) Hematologic events: e.g. lymphocytopenia: early: 17/62 (37.8); late: 23/62 (39.0) (grade 3), neutropenia: early: NR; late: 26/62 (42.6) (grade 4) Hepatic events: e.g. Alanine amino-transferase increased: early: 34/62 (54.8); late: 36/62 (58.1) (all grades)	
Safety: Bone marrow or haematological toxicity (6-8 week interval)										
2	Randomised controlled trial (n=1)	Very serious[c]	Very Serious[116]	Serious[109]	Very serious[110]	Publication bias (undetected) Large effect (no) Plausible confounding (no) Dose response gradient (no)	44	49	*Peri-procedural events*: Cardiac toxicity was manifested by elevated troponin 6/70 (8.6), sinus tachycardia 2/70 (2.9), myocardial infarction 1/70 (1.4), atrial fibrillation 1/70 (1.4), pericardial effusion 1/70 (1.4), ventricular tachycardia 1/70 (1.4), renal toxicity 0/70 (0) *Post-procedural events:* were related to effects of bone marrow suppression	Very low[114]
	Prospective, single-centre, single-arm observational study (n=1)						35		Increase of aminotransferases indicated some degree of hepatic toxicity; p<0.01	

[113] Inconsistency in the results (RCT: 90% grade 3 events, observational studies 21% and 39% grade 3 events).

[114] High risk of bias (-2), inconsistency (-2), indirectness (-1), imprecision (-2).

[115] serious adverse events from above are incorporated.

[116] Inconsistency in results.

Quality assessment							Summary of findings			
							Number of patients		Effect	Quality
Number of articles	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melphalan Percutaneous hepatic perfusion	Best alternative care	Absolute (95% CI) or n (%)	
Safety: Discontinuation of therapy (6-8 week interval)										
2	Randomised controlled trial (n=1)	Very serious[c]	Very serious[116]	Serious[109]	Very serious[110]	Publication bias (undetected) Large effect (no) Plausible confounding (no) Dose response gradient (no)	44	49	Disease progression: 20/70 (28.6) Adverse events: 24/70 (34.3) Patient decision: 1/70 (1.4) Investigator's opinion: 9/70 (12.9) Lost to follow-up: 0/70 (0) Completed four cycles of therapy and no clinical indication to continue: 5/70 (7.1) Completed six cycles of PHP therapy or equivalent of best alternative care (twelve 3-week cycles): 2/70 (2.9) Other: 6/70 (8.6)	Very low[114]
	Prospective, single-centre, single-arm observational study (n=1)						35		n=5/67 procedures	

Abbreviations: IG – intervention group, CG – control group.

Comments:

[a] *Using the Cochrane Collaboration tool version 2, 1 RCT with high risk of bias. High risk of bias is arising from the randomisation process and from the lack of measurements of the outcomes.*

[b] *Using the IHE RoB checklist, 1 study (RCT) with high risk of bias, 2 studies (prospective, single-centre, single-arm observational studies) with moderate risk of bias. Serious limitations are given due to the lack of information concerning the randomisation process, lack of measurements of the outcomes (RCT), single-centre design, and patients entering into the study at a different point in disease (observational studies).*

[c] *Using the IHE RoB checklist, 1 study (RCT) with high risk of bias, 1 study (prospective, single-centre, single-arm observational study) with moderate risk of bias. Serious limitations are given due to the lack of information concerning the randomisation process, lack of measurements of the outcomes (RCT), single-centre design, and patients entering into the study at a different point in disease (observational study).*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Applicability table

Table A-7: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The target population of this report included all patients with unresectable primary and/or secondary liver cancer. Patients (n=128, age range 31-77 years) suffering from unresectable ocular or cutaneous melanoma metastatic to the liver were enrolled in the trials. Only secondary liver cancer patients were enrolled due to higher prevalence than primary liver cancer. Inclusion criteria were primarily histologically proven, unresectable ocular melanoma metastases confined to the liver.
Intervention	The medical device Hepatic CHEMOSAT® Delivery System manufactured by Delcath Systems Inc., Queensbury, NY, USA, has been developed as an alternative non-operative treatment. Chemosaturation with percutaneous hepatic perfusion represents a repeatable and minimally invasive hepatic therapy technique where the liver is isolated from the systemic circulation. This system delivers a high dose of the chemotherapeutic agent melphalan directly to the liver, and, therefore, systemic exposures are limited. However, in contrast to isolated hepatic perfusion, in percutaneous hepatic perfusion, some leak of the therapeutic agent into the systemic circulation occurs because the vascular isolation of the liver is not achieved completely. A specific filter system extracorporeally filters the blood before it is returned to the systemic circulation, allowing a complete melphalan washout in the liver. Differences in filters were present in the included studies as filter generations 1 and 2 were used. This may affect the generalisability derived from safety results and raise applicability concerns regarding the intervention.
Comparators	The comparator was best available care, e.g., systemic chemotherapy, embolisation, supportive care. Best available care reflects best alternative treatments used in the treatment of unresectable primary or secondary liver cancer.
Outcomes	Crucial, patient-relevant *efficacy* outcomes such as overall survival, overall and hepatic (primary endpoint in included study) progression-free survival, and additional important outcomes, i.e., hepatic objective response and objective response rate, were most frequently reported. Quality of life as a crucial outcome was not assessed. The most commonly reported important *safety* outcomes were procedure-related complications, bone marrow or haematological toxicity, discontinuation of therapy, and the crucial outcome death. Efficacy outcomes were reported over six week ± 2-week intervals while receiving active treatment, and safety outcomes over six to eight week intervals. Regarding safety outcomes, no standardised reporting was available. They were described for patients *or* procedures and different grades of events, which cannot be compared. Furthermore, they were counted only on the number and percentages of patients, which also may affect the generalisability derived from safety results. As a result, the applicability for safety is limited and must be interpreted with caution. The measured outcomes and timing reflect the most important clinical benefits and harms.
Setting	One study was conducted in the United States, and two articles came from the same Dutch study. It is not expected that geographic settings limit the applicability of the results. Treatments occurred in an inpatient setting in all included trials, representing the settings in which the intervention will be typically used. Percutaneous hepatic perfusion is performed in interventional radiology suites or operating rooms with fluoroscopic imaging capability. A multidisciplinary team and special premises are needed for using the Delcath Hepatic CHEMOSAT® Delivery System.

List of ongoing randomised controlled trials

Table A-8: List of ongoing randomised controlled trials of percutaneous hepatic perfusion (PHP)

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT03086993 (EudraCT number 2016-003812-10)	Patients with intrahepatic cholangiocarcinoma (patients with cancer of the bile ducts in the liver)	Melphalan (hepatic delivery system) treatment given sequentially following cisplatin/ gemcitabine	Cisplatin/ Gemcitabine (standard of care)	Overall survival	End of trial status: ongoing	Delcath Systems Inc.

Research questions

Table A-9: Health problem and current use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table A-10: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications have the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-11: Clinical effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?

Table A-12: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?

Literature search strategies

Search strategy for Medline via Ovid

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 15, 2021>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2017 to December 15, 2021>	
Search date: 16.12.2021	
ID	Search
1	exp Liver Neoplasms/ (211860)
2	((liver or hepatic or hepato*cell* or hepato-cell*) adj4 (secondar* or cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or adeno-c* or neoplasm* or sarcoma* or h?emangioma* or malignan* or lump* or mass$2 or metasta*)).mp. (340128)
3	hepatoma*.mp. (33288)
4	exp Cholangiocarcinoma/ (14023)
5	cholangio?carcinoma*.mp. (24241)
6	cholangio-carcinoma*.mp. (96)
7	hepato?carcinoma*.mp. (5527)
8	hepato-carcinoma*.mp. (62)
9	HCC.ti,ab. (94266)
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (372367)
11	exp Chemotherapy, Cancer, Regional Perfusion/ (4228)
12	((percut* or isolate*) adj4 (hepat* or liver*) adj4 (perfus* or chemo?perfus* or chemo-perfus*)).mp. (5040)
13	chemo?sat*.mp. (52)
14	chemo-sat*.mp. (0)
15	CS-PHP.ti,ab. (20)
16	PHP.ti,ab. (3222)
17	PIHP.ti,ab. (49)
18	exp Melphalan/ (8668)
19	melphalan*.mp. (12769)
20	Delcath*.mp. (21)
21	((hepat* or liver*) adj4 (vein* or venous* or arter* or outflow*) adj4 (isolat* or segregate*)).mp. (329)
22	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (24490)
23	10 and 22 (1117)
24	limit 23 to dt=20201215-20211216 (39)
25	limit 24 to (english or german) (39)
26	remove duplicates from 25 (21)
Total hits: 21	

Search strategy for Embase

Search Name: Chemosaturation with hepatic perfusion/isolation for liver cancer		
Comment: LG/VH		
Search date: 16.12.2021		
No.	Query Results	Results
#29	#27 NOT #28	157
#28	#27 AND 'Conference Abstract'/it	44
#27	#26 AND ([english]/lim OR [german]/lim)	201
#26	#25 AND [15-12-2020]/sd NOT [17-12-2021]/sd	202
#25	#12 AND #24	3,420
#24	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	60,643

#23	(hepat* OR liver*) NEAR/4 (vein* OR venous* OR arter* OR outflow*) NEAR/4 (isolat* OR segregate*)	373
#22	delcath*	89
#21	melphalan*	41,907
#20	'melphalan'/exp	40,448
#19	pihp:ti,ab	55
#18	php:ti,ab	4,779
#17	'cs-php':ti,ab	27
#16	'chemo-sat*'	21
#15	chemo*sat*	2,124
#14	(percut* OR isolate*) NEAR/4 (hepat* OR liver*) NEAR/4 (perfus* OR chemo*perfus* OR 'chemo-perfus*')	5,438
#13	'liver perfusion'/exp	8,947
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	453,771
#11	hcc:ti,ab	102,395
#10	'hepato-carcinoma*'	80
#9	hepato*carcinoma*	6,950
#8	'hepatocellular carcinoma cell line'/exp	11,333
#7	'cholangio-carcinoma*'	189
#6	cholangio*carcinoma*	25,148
#5	'bile duct carcinoma'/exp	32,579
#4	hepatoma*	38,098
#3	'liver cell carcinoma'/exp	183,067
#2	(liver OR hepatic OR hepato*cell* OR 'hepato-cell*') NEAR/4 (secondar* OR cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR 'adeno-c*' OR neoplasm* OR sarcoma* OR hemangioma* OR haemangioma* OR malignan* OR lump* OR mass* OR metasta*)	396,590
#1	'liver tumor'/exp	326,287

Search strategy for The Cochrane Library

Search Name: Chemosaturation with hepatic perfusion/isolation for liver cancer	
Last saved: 16/12/2021 19:37:30	
Comment: MEL 2022 (LG/CW) 161221	
ID	Search
#1	MeSH descriptor: [Liver Neoplasms] explode all trees
#2	((liver OR hepatic OR hepato*cell* OR hepato-cell*) NEAR (secondar* OR cancer* OR tumo?r* OR carcinom* OR adenom* OR adeno?c* OR neoplasm* OR sarcoma* OR h?emangioma* OR malignan* OR lump* OR mass* OR metasta*)) (Word variations have been searched)
#3	(hepatoma*) (Word variations have been searched)
#4	MeSH descriptor: [Cholangiocarcinoma] explode all trees
#5	(cholangio?carcinoma*) (Word variations have been searched)
#6	(cholangio-carcinoma*) (Word variations have been searched)
#7	(hepato?carcinoma*) (Word variations have been searched)
#8	(hepato-carcinoma*) (Word variations have been searched)
#9	(HCC):ti,ab,kw (Word variations have been searched)
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	MeSH descriptor: [Chemotherapy, Cancer, Regional Perfusion] explode all trees
#12	((percut* OR isolate*) NEAR (hepat* OR liver*) NEAR (perfus* OR chemo?perfus* OR chemo-perfus*)) (Word variations have been searched)
#13	(chemo?sat*) (Word variations have been searched)
#14	(chemo-sat*) (Word variations have been searched)
#15	(CS-PHP):ti,ab,kw (Word variations have been searched)

#16	(PHP):ti,ab,kw (Word variations have been searched)
#17	(PIHP):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Melphalan] explode all trees
#19	(melphalan*) (Word variations have been searched)
#20	(Delcath*) (Word variations have been searched)
#21	((hepat* OR liver*) NEAR (vein* OR venous* OR arter* OR outflow*) NEAR (isolat* OR segregate*)) (Word variations have been searched)
#22	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	#10 AND #22
#24	#23 with Cochrane Library publication date Between Dec 2020 and Dec 2021
#25	#23 with Publication Year from 2020 to 2021, in Trials
#26	#24 OR #25
#27	(conference abstract):pt (Word variations have been searched)
#28	(abstract):so (Word variations have been searched)
#29	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so (Word variations have been searched)
#30	#27 OR #28 OR #29
#31	#26 NOT #30
Total hits: 0	

Search strategy for CRD (DARE, NHS-EED, HTA)

Search Name: Chemosaturation with hepatic perfusion/isolation for liver cancer	
Search date: 16.12.2021	
ID	Search
18	(((HCC) OR (hepatocarcinoma*) OR (hepatoma*) OR (cholangiocarcinoma*) OR ("Cholangiocarcinoma"[mhe]) OR (liver OR hepatic OR hepatocell*) OR ("Liver Neoplasms"[mhe])) AND ((PIHP) OR (PHP) OR (CS-PHP) OR (Delcath*) OR (perfus* OR chemoperfus* OR percut* OR isolat* OR segregat* OR chemosat*) OR ("Melphalan"[mhe]) OR ("Chemotherapy Cancer Regional Perfusion"[mhe])))) FROM 2020 TO 2021,"0","2021-12-16T19:10:06.000000Z"
17	((HCC) OR (hepatocarcinoma*) OR (hepatoma*) OR (cholangiocarcinoma*) OR ("Cholangiocarcinoma"[mhe]) OR (liver OR hepatic OR hepatocell*) OR ("Liver Neoplasms"[mhe])) AND ((PIHP) OR (PHP) OR (CS-PHP) OR (Delcath*) OR (perfus* OR chemoperfus* OR percut* OR isolat* OR segregat* OR chemosat*) OR ("Melphalan"[mhe]) OR ("Chemotherapy Cancer Regional Perfusion"[mhe])),"25","2021-12-16T19:09:23.000000Z"
16	(HCC) OR (hepatocarcinoma*) OR (hepatoma*) OR (cholangiocarcinoma*) OR ("Cholangiocarcinoma"[mhe]) OR (liver OR hepatic OR hepatocell*) OR ("Liver Neoplasms"[mhe]),"372","2021-12-16T19:09:02.000000Z"
15	HCC,"27","2021-12-16T19:08:47.000000Z"
14	hepatocarcinoma*,"4","2021-12-16T19:08:35.000000Z"
13	hepatoma*,"1","2021-12-16T19:08:16.000000Z"
12	cholangiocarcinoma*,"6","2021-12-16T19:07:48.000000Z"
11	"Cholangiocarcinoma"[mhe],"4","2021-12-16T19:07:40.000000Z"
10	liver OR hepatic OR hepatocell*,"368","2021-12-16T19:07:19.000000Z"
9	"Liver Neoplasms"[mhe],"87","2021-12-16T19:03:12.000000Z"
8	(PIHP) OR (PHP) OR (CS-PHP) OR (Delcath*) OR (perfus* OR chemoperfus* OR percut* OR isolat* OR segregat* OR chemosat*) OR ("Melphalan"[mhe]) OR ("Chemotherapy Cancer Regional Perfusion"[mhe]),"599","2021-12-16T19:01:45.000000Z"
7	PIHP,"0","2021-12-16T19:01:35.000000Z"
6	PHP,"0","2021-12-16T19:01:28.000000Z"
5	CS-PHP,"0","2021-12-16T19:01:22.000000Z"
4	Delcath*,"1","2021-12-16T19:00:21.000000Z"
3	perfus* OR chemoperfus* OR percut* OR isolat* OR segregat* OR chemosat*,"588","2021-12-16T18:59:37.000000Z"
2	"Melphalan"[mhe],"4","2021-12-16T18:55:24.000000Z"
1	"Chemotherapy Cancer Regional Perfusion"[mhe],"7","2021-12-16T18:54:49.000000Z"
Total hits: 0	

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH